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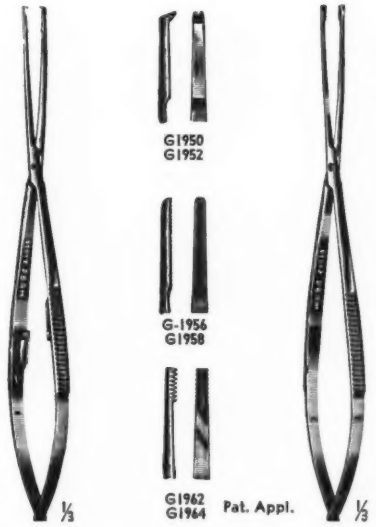

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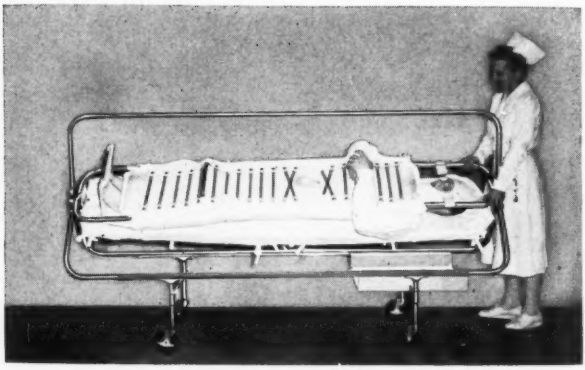

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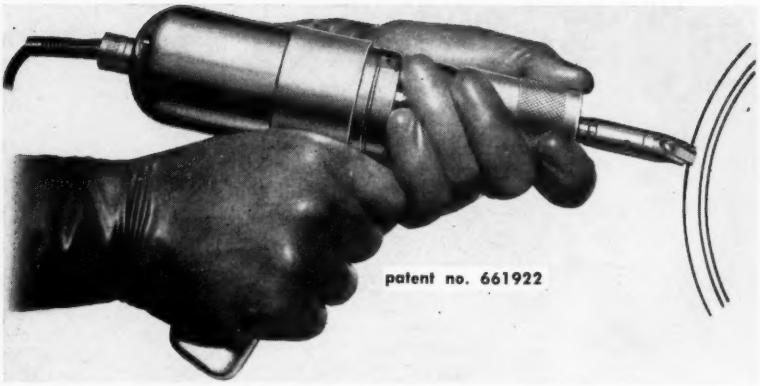

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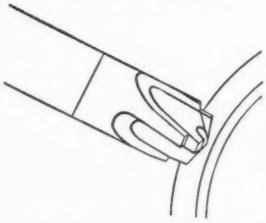

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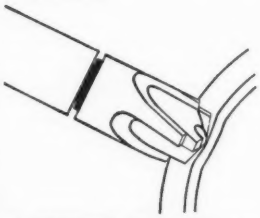

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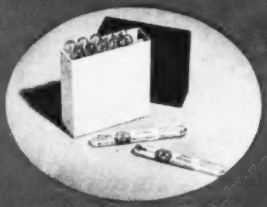

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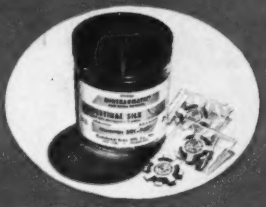

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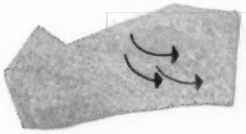

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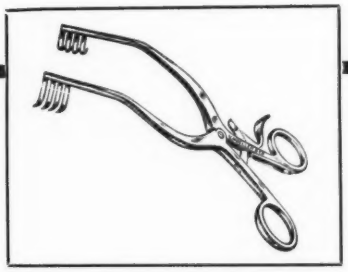

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PREFACE

This is the first volume of a new series entitled «Progress in Cardiology». The object of this series is to publish at convenient intervals, monographs dealing with cardiological problems of topical interest. It is proposed that a particular subject will be discussed from various angles by several authors who, in view of personal contributions or special experience, are experts. Such monographs, it is hoped, will be a convenient and time-saving means of providing the reader with a comprehensive and up to date account of our knowledge in the various fields; for this purpose critical reviews have been rendered indispensable by the vast number of scattered publications. This series is not intended for the publication of individual papers suitable for specialised journals, but is planned as a series of monographs each devoted to one particular subject. Its aim is thus to contribute to the synthesis of problems by providing reviews which summarize particular topics, thereby assisting cardiologists in their scientific and practical work.

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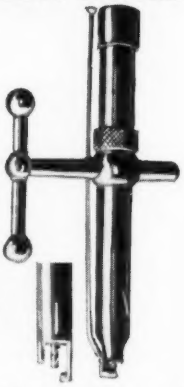

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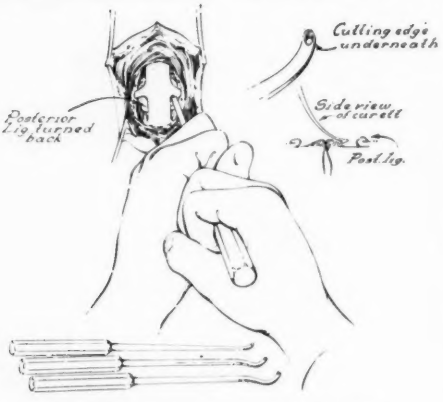

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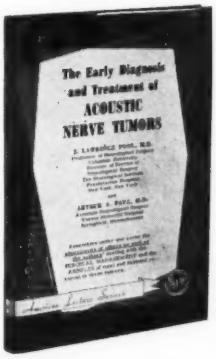

THE EARLY DIAGNOSIS AND TREATMENT OF ACOUSTIC NERVE TUMORS

By

J. LAWRENCE POOL, M.D.
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Columbia University
Director of Service of Neurological Surgery
The Neurological Institute
Presbyterian Hospital
New York, New York

and

ARTHUR A. PAVA, M.D.
Assistant Neurological Surgeon
Wesson Memorial Hospital
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Attending Neurological Surgeon, Montefiore Hospital, and Professor and Chairman, Department of Surgery, Albert Einstein College of Medicine, New York City

WITH an average of more than one color plate per page, this authoritative one-volume atlas depicts both *gross and microscopic features of all tumors of the brain, spinal cord and peripheral and sympathetic nervous systems.* Full attention is devoted, also, to space-occupying lesions such as infectious granulomas and metastatic tumors. The extensive use of color in this beautifully printed book serves two practical purposes: *1,* It enables all who use it to compare their own specimens with the diagnostic illustrations; *2,* It becomes an actual and highly desirable substitute for the insufficient quantity of tumor material of the nervous system that is available in most medical centers. In addition to the profuse *diagnostic guidance* this atlas contains, there is full consideration of the biologic behavior, incidence, localization, treatment and prognosis of the neoplasms discussed. The effects of increased intracranial pressure on the brain are covered in detail.

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191 Pages, 7" × 10". 277 Illustrations, 233 in Color. 4 Tables. $25.00

(Published November, 1956)

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THE VARYING EXPRESSIONS OF EMBRYONAL ATRESIA OF THE FOURTH VENTRICLE IN ADULTS

ARNOLD-CHIARI MALFORMATION, DANDY-WALKER SYNDROME, "ARACHNOID" CYST OF THE CEREBELLUM, AND SYRINGOMYELIA*

W. JAMES GARDNER, M.D., A. F. ABDULLAH, M.B., CH.B.,† AND LAWRENCE J. McCORMACK, M.D.

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(Received for publication January 24, 1957)

IN ADULTS the clinical picture of the Arnold-Chiari malformation may be indistinguishable from that of congenital atresia of the foramen of Magendie (a diverticulum of the fourth ventricle referred to by Benda[1] as the "Dandy-Walker syndrome"). The clinical picture of Arnold-Chiari malformation also is indistinguishable from that of certain "arachnoid" cysts of the cerebellum and from that of syringomyelia. Features that may be encountered in these four pathologic entities are basilar impression, scoliosis, hydromyelia, a band of thickened meninges constricting the structures at the level of the foramen magnum, and obstruction of the outlets of the fourth ventricle by membranes, the attachments of which indicate that they are persisting remnants of the embryonic rhombic roof. Having so many rare features in common, it seems likely that these four pathologic entities are merely varying expressions of the same disease produced by a common cause. That cause, we believe, is failure of the outlets of the fourth ventricle to develop normally in the rhombic roof of the embryo. The term "embryonal" is more descriptive than is "congenital" for this condition, because the membrane responsible for atresia undergoes differentiation in embryonic life.

In 1950 Gardner and Goodall[7] described 17 patients between the ages of 14 and 54 years in whom an Arnold-Chiari malformation was disclosed at operation. Eight of these patients had basilar impression and 8 had scoliosis. The exposed portion of the cervical cord was hydromyelic in 13 of these patients, and in several of them there was a band of thickened meninges which appeared to be constricting the intradural structures at the level of the foramen magnum. A foraminal hernia with obstruction of the

* Presented at the meeting of the Harvey Cushing Society, Detroit, Michigan, April 27, 1957.

† Formerly Fellow in the Department of Neurological Surgery, The Cleveland Clinic Foundation; present address: 132 N. Potomac Ave., Hagerstown, Md.

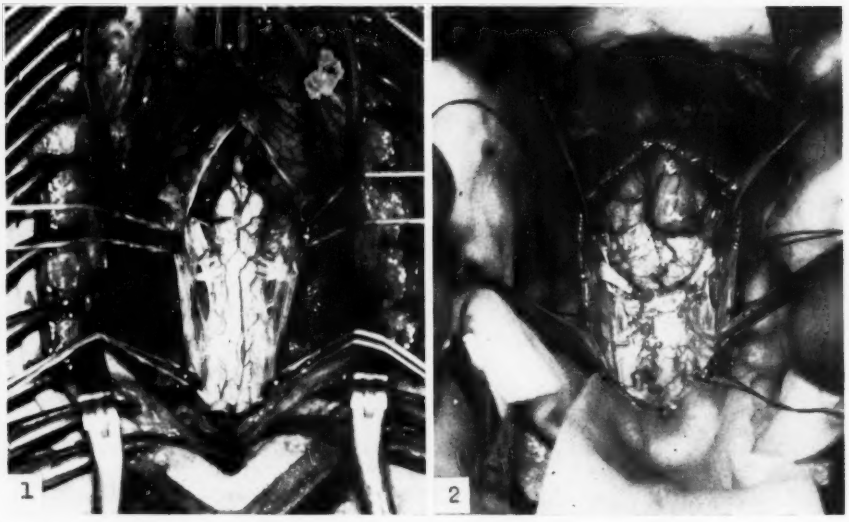


FIG. 1. Occipitocervical exposure showing relationship of normal structures. The arachnoid of the cisterna magna has been incised. The obex is visible through the foramen of Magendie between the cerebellar tonsils. The 2nd cervical nerve roots pursue a slightly caudad direction to their foramens of exit.

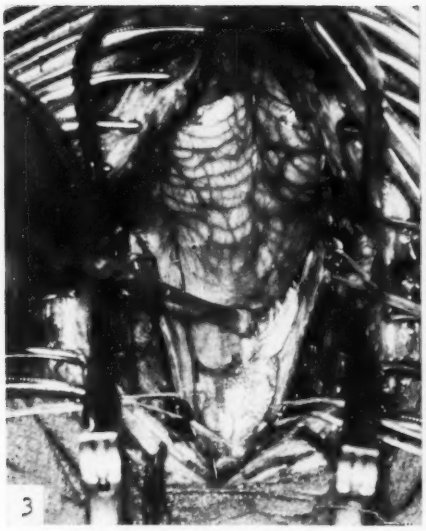
FIG. 2. Woman aged 20 years with dissociated sensory loss, basilar impression, and scoliosis. Obstruction of the foramen of Magendie is present but hydromyelia could not be demonstrated. The dentate ligaments appear to be resisting the caudal dislocation of the upper cervical cord.

foramen of Magendie was demonstrated in every patient, and surgical release of this obstruction generally was followed by symptomatic improvement (Figs. 1–9).

Since publication of that report, the above-described features that we considered pathognomonic of the adult form of the Arnold-Chiari malformation have been observed in one patient with the typical operative findings of the Dandy-Walker syndrome, in another with so-called arachnoid cyst of the cerebellum, and in still another with syringomyelia. A membrane attached to the margins of the foramen of Magendie was demonstrated in each of these patients. These findings led to an inspection of the foramen of Magendie during subsequent operations for the Arnold-Chiari malformation, and a careful separation of the adherent tonsils has disclosed a similar membrane separate from the arachnoid in most instances.

An example of atresia of the foramen of Magendie was excellently described and illustrated by Dandy and Blackfan[5] in 1914 (Fig. 10). These authors referred to the lesion as a *dilated fourth ventricle*, and so it appears to be in the severe infantile form. However, a study of the less severe cases encountered in adults shows that *diverticulum** is a more nearly accurate

* Diverticulum—a pouch or pocket leading off from a main cavity or tube.—Dorland's Illustrated Medical Dictionary, 23rd Edition, page 407.



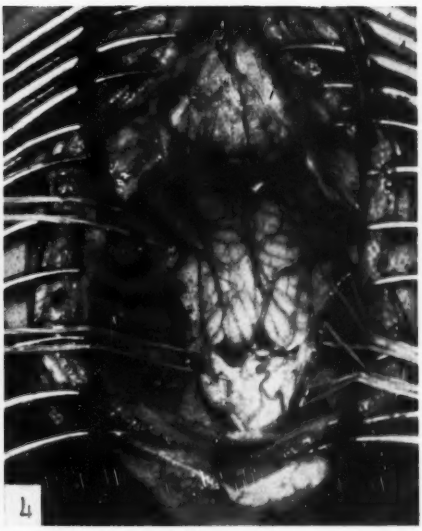


FIG. 3. Woman aged 44 years with loss of hearing for 25 years and cerebellar symptoms for 8 years. There was basilar impression. Note cephalad course of 2nd cervical nerve roots. There was no dissociated sensory loss and the exposed portion of the cord was not cystic.

FIG. 4. Man aged 42 years with progressive left hemiparesis, no basilar impression, and congenital fusion of C3 and C4. Encephalography disclosed filling defect in the cisterna magna, no air in the ventricles. There is marked hydromyelia despite the absence of dissociated sensory loss. The symptoms were relieved and postoperative encephalogram showed normal ventricles.

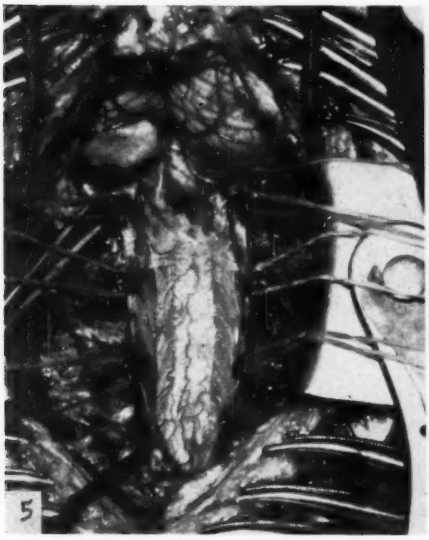


FIG. 5. Girl aged 14 years with dissociated sensory loss and scoliosis, but with no basilar impression. A moderately thickened arachnoid constricts the structures at and below the foramen magnum. The tonsils are herniated; hydromyelia is present.

FIG. 6. Same case as in Fig. 5. The cerebellar tonsils have been separated and a membrane occluding the foramen of Magendie has been incised, exposing the obex. This structure is found to be above the level of the foramen magnum and therefore herniation of the brain stem has not occurred.

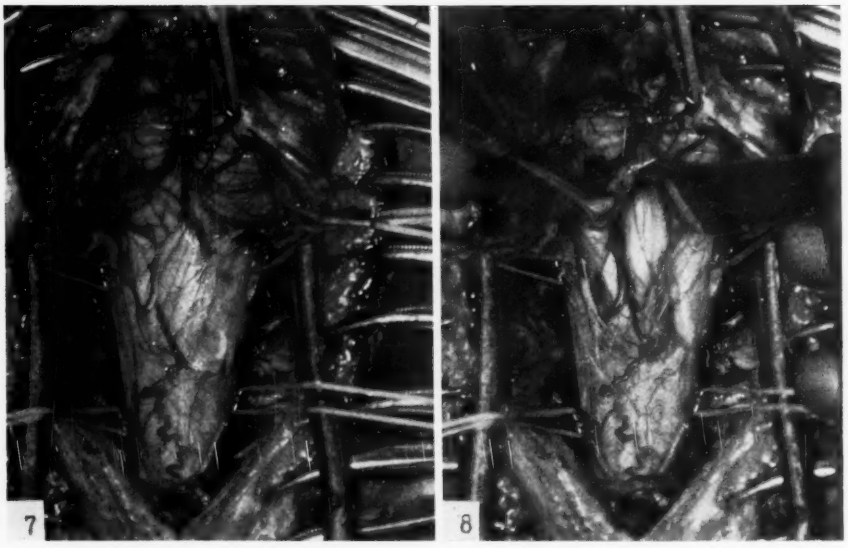


FIG. 7. Man aged 27 years with occipital headache, sensory loss in C2 and bilateral astereognosis; no basilar impression. At encephalography the spinal air column stopped at C3; there was no air in the ventricles.

FIG. 8. Same case as in Fig. 7. The tonsils were adherent to each other but an actual membrane was not described. The obex was at C2. The exposed portion of the cord was not cystic.

term. In the infantile forms, the cerebellar hemispheres are widely separated; there may be total absence of the vermis of the cerebellum; and there is a bulging posterior fossa with failure of the lateral sinuses and attached tentorium to descend from their fetal position. Taggart and Walker[15] studied the pathogenesis of this condition and concluded that the cause of the typical deformity was failure of the foramen of Magendie to open during intrauterine life. They believe, and we agree, that the associated cerebellar lesions, although prominent, are the *result* of the hydrocephalus. Gibson,[8] in reporting 3 new cases in addition to the 24 previously reported, also favored Taggart and Walker's[15] conclusion. Benda,[1] on the other hand, believed that the lesion belonged to the category of cleft formations or rachischisis, and that the essential fault was not in the failure of the apertures to open, but failure of the dorsal midline to fuse. His argument, however, is controverted by the lack of cleft in the milder adult forms of this lesion.

Case 1.—Diverticulum of the Foramen of Magendie (Dandy-Walker Syndrome).

A 24-year-old woman was admitted on Sept. 16, 1955, with a presenting complaint that she "fell a lot." Six or 7 years prior to admission she had a bout of severe headache lasting several weeks. Afterward, the right eye turned in, and awkwardness of all extremities gradually developed. For 1 year she had experienced difficulty in enunciating, had fallen frequently, and had burned herself on the arms and hands without being aware of it.

Examination revealed scoliosis of the thoracic spine. There was right internal strabismus. The optic disks were normal. The tongue was atrophied on the left side, the gag reflex was absent, and the speech had a bulbar quality. The deep tendon reflexes were absent in the upper extremities and hyperactive in the lower extremities, but Babinski's sign was absent. There was atrophy of the small muscles of both hands. Sensory studies disclosed impairment of appreciation of pain, temperature, and vibration, from the 2nd cervical to the 5th thoracic dermatomes. Light touch appreciation and stereognosis were intact. Roentgenograms showed exaggerated cervical lordosis and basilar impression with the tip of the dens 13 mm. above McGregor's line.*

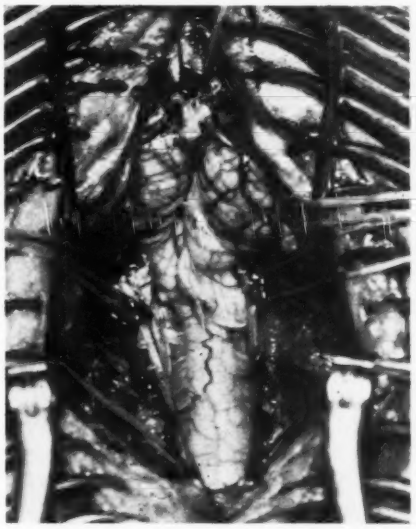


FIG. 9. Woman aged 41 years with dissociated sensory loss, basilar impression and scoliosis. The tonsils were adherent but a membrane obstructing the foramen of Magendie was not described. The cystic spinal cord appeared to have dilated the spinal canal.

Because of the basilar impression, the scoliosis, and the clinical picture suggesting syringobulbia, an unqualified diagnosis of Arnold-Chiari malformation was made.

In order to study the mechanics of this condition, it has been our custom to inject dye into the lateral ventricle, to follow this by encephalography, and then at operation to aspirate fluid from the hydromyelic sac to ascertain whether it is continuous with the ventricular system. Accordingly, on Oct. 10, 1955, 2 ml. of indigo-carmine was injected into the right lateral ventricle through a burr hole. Five minutes later, pneumoencephalography was performed in the operating room.† With the patient in the sitting position, the initial spinal fluid pressure was 350 mm. of water. The vertex of the skull was 600 mm. above the level of the spinal needle. After 45 ml. of fluid had been replaced with 60 ml. of air, the spinal canal was empty. Indigo-carmine appeared in the second 10 ml. of fluid removed. The protein content of the fluid was 17.5 mg. per 100 ml. The films showed air partially outlining dilated lateral ventricles and a bubble of air beneath the tentorium. There was air nowhere else within the cranial cavity. The cisterna magna was quite small but a definite foraminal hernia could not be seen in it.

---

* McGregor's line is a line drawn from the posterior end of the hard palate to the lowest portion of the occipital bone.[12] We prefer to use it in place of Chamberlain's line which is drawn from the hard palate to the posterior rim of the foramen magnum, because the latter structure is displaced upward with the rest of the base of the skull and may be difficult to see.

† Since 1929, pneumoencephalography at the Cleveland Clinic Hospital has been performed *only* in the operating room. For the patient's safety, the air injection, the roentgenography, and the development of the films is done nowhere else. An anesthetist is in constant attendance; two sterile packs of instruments are available, one for emergency ventricular tap and the other for craniotomy. The films are developed in a rapid developer and if a surgical lesion is disclosed, operation follows at once. Films are always made with the patient in the upright position for adequate visualization of the cisterna magna.

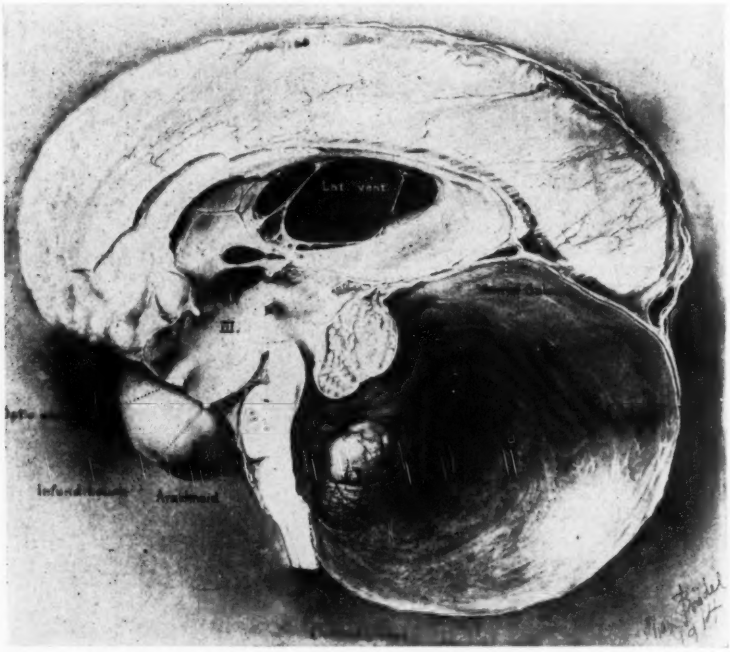


FIG. 10. Diverticulum of the foramen of Magendie. The artist's reconstruction of the case of Dandy and Blackfan[5] illustrates a significant point that frequently is overlooked; namely, the attachment of the membrane to the obex and taenia of the fourth ventricle.

Encephalography was followed immediately by an occipitovertebral decompression. A dense epidural band of fibrous tissue was found at the level of the foramen magnum. When the dura mater was incised, this band was found to have its counterpart in an adherent fibrous thickening of the arachnoid which appeared to be constricting the medulla. Above this band was a large cyst-like structure consisting of a translucent membrane distended by dye-stained fluid. Through it, the cerebellar lobes could be seen to be displaced laterally and upward. When the presumed cyst was opened, the floor of the fourth ventricle lay exposed (Fig. 11). At the obex, the upper end of the central canal could be seen to be dilated into a funnel shape. Below the medulla the spinal cord was cystic, and an aspirating needle introduced into it recovered dye-stained fluid. It became obvious that this was a case of atresia of the foramen of Magendie, and that the cyst-like structure actually was a diverticulum of the fourth ventricle formed by the distended membrane that closed the foramen. It was apparent, too, that the hydromyelic sac communicated with the obstructed fourth ventricle. The sac was not incised. Histologically, the thin excised membrane was dense and fibrous. Several melanocytes were enmeshed in its interstices. No inflammatory reaction was present.

The postoperative course was uneventful. Two months later the patient was greatly improved, although still ataxic. The sensory loss was limited to impaired thermal perception in the left hand and over the right arm.

Comment. In this case the presence of dye in the spinal fluid conceivably could have occurred by dialysis through the attenuated membrane of the diverticulum. However, the presence of air in the ventricles proved that there was an anatomic communication between the ventricles and the subarachnoid space. Such communication has been reported in other cases. Since it is unlikely that a bulging diverticulum would develop unless the atresia originally included all three outlets, it has been attributed to delayed opening of one of the foramens. The history in the above case suggests that such a spontaneous perforation of a foramen of Luschka may have occurred 6 or 7 years before admission, when the headache of several weeks' duration cleared spontaneously. If such were the case, why then was there

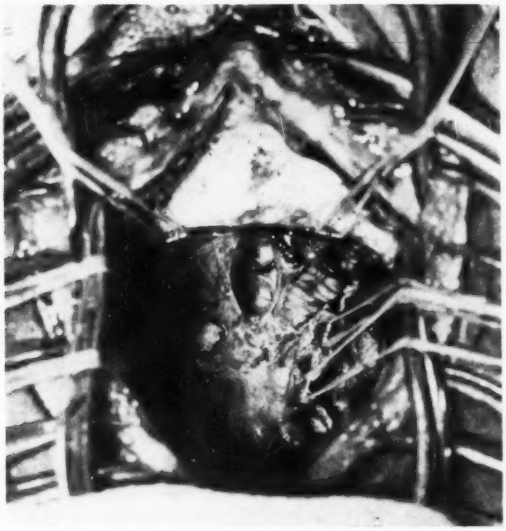


FIG. 11. *Case 1.* This shows the dilated foramen of Magendie after the diverticulum had been excised. Note the thickened arachnoid at the level of the foramen magnum. The hydromyelic sac has collapsed.

subsequent progression of neurological symptoms? The improvement that followed the surgical establishment of a patent foramen of Magendie suggests that there was a cause-and-effect relation and, therefore, that patency of the midline foramen is more important than patency of the laterally placed and devious foramens of Luschka. The reason for this, we believe, is that the foramen of Magendie is in direct line with the aqueduct and therefore is in a more advantageous position to permit a spinal subarachnoid dissipation of the ventricular fluid pulse wave as it spurts from the aqueduct with each heart beat. When this midline foramen fails to open, the pounding of the ventricular fluid pulse wave is funneled toward the upper end of the central canal and results in gradual hydromyelic

distention of the canal at a lower level of lesser resistance. Conversely, when the ventricular fluid pulse wave is dissipated freely in the subarachnoid space through a patent foramen of Magendie, this effect is reversed, the pulse wave tending to compress the cord from without rather than to dilate it from within.

The thickening of the meninges at the level of the foramen magnum is caused by mechanical trauma as the structures are impacted into the foramen magnum with each ventricular systole.

Hydromyelia has not been described in other reported cases of Dandy-Walker syndrome, perhaps because usually it has not been sought. Gibson,[8] however, described a funnel-shaped entrance to the central canal in his 2 patients, and the photographs in 2 cases reported by Taggart and Walker[15] suggest the same thing.

The above case is the only instance of diverticulum of the foramen of Magendie that we have recognized in an adult. This patient exhibited five features that we have come to associate with the Arnold-Chiari malformation, namely, basilar impression, scoliosis, hydromyelia, meningeal thickening and an occluding membrane attached to the margins of the foramen of Magendie.

Case 2.—Cyst of Foramen of Magendie ("Arachnoid" Cyst of the Cerebellum).

A 24-year-old man was seen on July 26, 1954, for emergency treatment, because of episodes of respiratory arrest. He was known to have scoliosis and a paresis of the left leg since infancy. For 2 months, during sleep he had exhibited noisy respiration with long periods of apnea. Two days before admission he was found deeply cyanotic, apneic, and unconscious. Subsequent episodes of respiratory arrest had been treated in another hospital by artificial respiration.

On examination, the patient was cyanotic; his respirations were slow and stertorous. He responded sluggishly to commands but there was no reaction to pinpricks anywhere over the surface of the skin. There was no papilledema. There were left hemiplegia, coarse nystagmus, and he was unable to swallow. He was sweating freely on the right side of the face but not on the left. The Babinski's and Hoffmann's signs were present bilaterally. There was scoliosis of the thoracic spine. On the basis of these findings the clinical diagnosis was Arnold-Chiari malformation.

The patient was brought immediately to surgery where, under thiopental sodium anesthesia, an endotracheal tube was inserted, preparations were made for a ventricular tap, and encephalography was performed. The spinal fluid pressure was normal; only 50 ml. of fluid was obtained. The resulting encephalograms showed no air in the ventricular system, and the distribution of the subarachnoid air indicated an advanced degree of obstructive hydrocephalus. Some of the air was trapped beneath the tentorium. A column of air outlined the spinal cord. The cisterna magna was small, suggesting that the foramen magnum was narrowed. The lamina of the 1st cervical vertebra was hypoplastic and appeared to be fused to the occipital bone. The tip of the dens was 12 mm. above McGregor's line, indicating well-marked basilar impression. The encephalographic findings agreed with the clinical diagnosis of Arnold-Chiari malformation (Fig. 12).

With the patient in the craniotomy chair in the sitting position, a cannula was introduced into a greatly dilated lateral ventricle, and 5 ml. of indigo-carmine was

injected. An occipitovertebral decompression was then performed. The lamina of the 1st cervical vertebra was in contact with but not fused to the foramen magnum. The foramen magnum, especially on the left side, was pushed inward, causing a deep indentation in the dura mater. When the dura mater was opened, the cerebellum appeared to have been largely replaced by a huge cyst filled with dye-stained fluid. An incision was made in the posterior wall of the cyst and its contents were evacuated. An intact anterior wall of the cyst was then disclosed roofing over the lower portion of the fourth ventricle, which suggested that dye from the ventricle had entered the cyst by dialysis through this membrane. At the level of the foramen

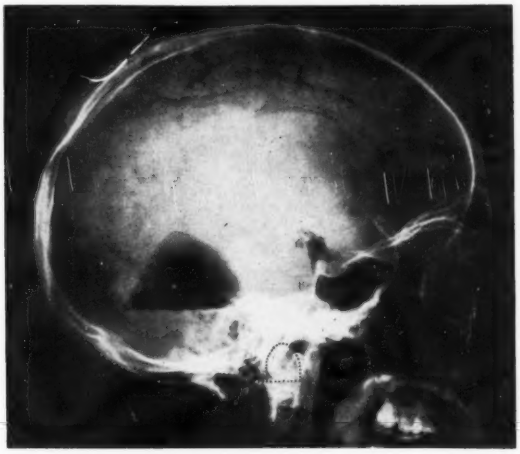


FIG. 12. *Case 2.* Encephalogram showing collection of subdural air trapped beneath the tentorium and the bulging supracallosal sulcus. There is basilar impression and "assimilation" of the lamina of C1. The small cisterna magna is poorly shown on this film.

magnum, and covering the medulla, there was a dense band of arachnoid tissue that appeared to separate the cranial cavity from the spinal canal. The 2nd cervical nerve roots pursued a cephalad course to their dural sleeves. The cerebellar tonsils were restrained within the cranial cavity by the dense band of tissue about the medulla. An incision was made in the anterior wall of the cyst above this band, releasing the pent-up ventricular fluid and disclosing the floor of the fourth ventricle. The operation was concluded.

The patient's condition remained critical after operation, requiring tracheotomy. Cheyne-Stokes breathing continued until the 2nd postoperative day when respiration stopped; resuscitative measures were unsuccessful.

Necropsy confirmed the operative findings. Injection of the aqueduct resulted in the escape of fluid only through an area corresponding to the right foramen of Luschka. The central canal of the cervical cord was found to be dilated (Fig. 13).

Histologically, the cyst wall was a mixture of fibrous tissue and glial elements with a thin lining of flattened cells resembling endothelium. Numerous foci of glial heterotopia were noted in the leptomeninges of the pons, the medulla, and the spinal cord.

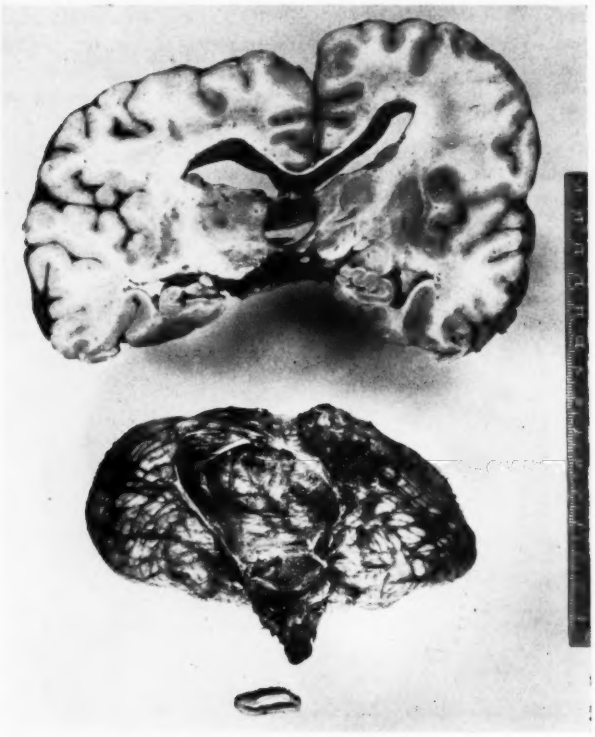


FIG. 13. *Case 2.* Gross specimen at necropsy.

Comment. The lesion in this case proved to be not a diverticulum but a true cyst attached to the margins of the foramen of Magendie. As in Case 1, the patient also presented the clinical picture of Arnold-Chiari malformation. Hydromyelia, though not seen at operation, was demonstrated at necropsy. This case closely resembles Case 1, in that scoliosis, basilar impression, a membrane obstructing the foramen of Magendie, and hydromyelia were present with a fibrous thickening of the arachnoid at the level of the foramen magnum.

Three other instances of cysts occluding the foramen of Magendie have been encountered. Photographs of 2 of these are shown in Figs. 14–17. In the past[3, 9–11] this expression of atresia has been referred to as "arachnoid cyst," as "cystic arachnoiditis," and in some cases perhaps has been mistaken for diverticulum. We believe that the lesion in this case differs from that encountered in Case 1 only in that the persisting portion of the rhombic roof had split into two layers to form a cyst; a mechanism similar to that which is responsible for the development of the subarachnoid spaces in the embryo, according to Weed.[17]

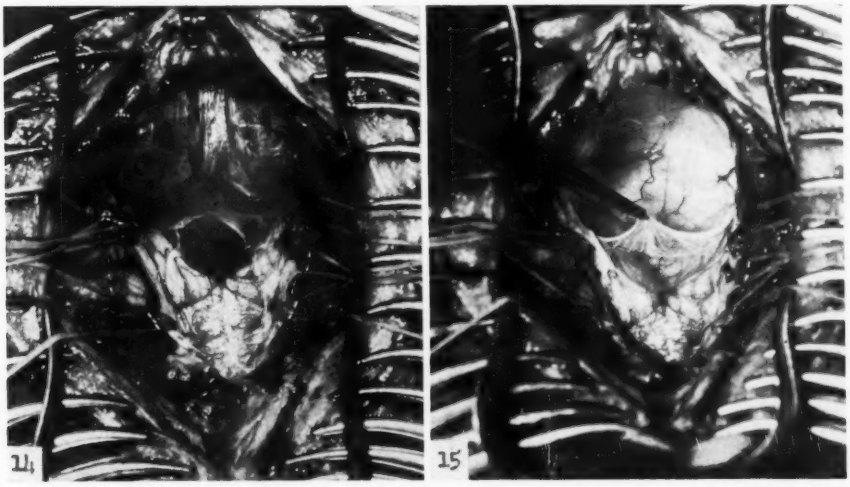


FIG. 14. Woman aged 55 years with a 10-year history of unsteady gait and recent bulbar symptoms. Cyst is attached to margins of the foramen of Magendie, but is separate from the arachnoid membrane. There is an associated Arnold-Chiari malformation.

FIG. 15. Same case as in Fig. 14. Cyst has been incised.

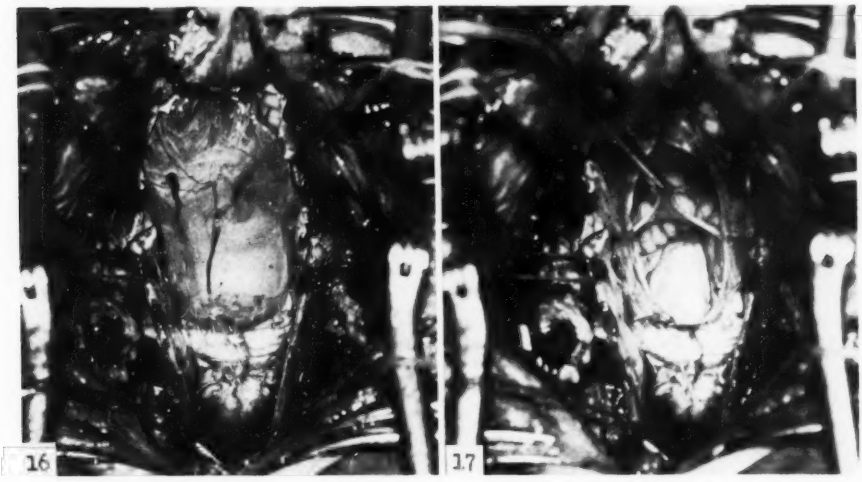


FIG. 16. Man aged 47 years with cerebellar and bulbar symptoms for 2 years. Dissociated sensory loss was present but the exposed portion of the cord was not cystic. Cyst is attached to margins of the foramen magnum.

FIG. 17. Same case as in Fig. 16. The inner and outer walls of the cyst have been incised and the inner wall is being held with forceps, disclosing the floor of the fourth ventricle beneath. The attachment of the cyst wall to the obex and taenia is clearly evident.

Case 3—Syringomyelia.

A 34-year-old woman with congenital scoliosis was seen on Feb. 23, 1955, because of a presenting complaint of weakness and numbness of both arms. Intermittent sensory symptoms had been present in the upper extremities for 10 years. Two years before admission, because of persistent numbness of the left thumb and index finger, a cervical laminectomy had been performed for syringomyelia. In the lower cervical region a cyst of the cord was found and incised. The patient stated that she was worse immediately after operation, having severe numbness of both hands and arms. For 6 months before the present admission she had progressive weakness of the upper extremities so that she was scarcely able to dress herself or to care for her 16-month-old baby. She had burned her hands unknowingly on several occasions. She had difficulty in walking, pain in the right buttock, constipation, hesitancy on urination, and loss of sensation in the vagina.

On neurological examination there was complete loss of appreciation of pain and temperature in both arms to a level above the elbows, and partial loss from the clavicles to the umbilicus. There was complete loss of sense of position in the hands, moderate impairment of perception of light touch, and the patient was unable to identify even large objects. Vibratory appreciation was lost below the clavicles. There were severe weakness of the upper extremities, atrophy of both deltoid muscles, and kyphoscoliosis of the thoracic spine. The patient walked with a slight limp on the right leg. Reflexes were absent in the upper extremities, as were the abdominal reflexes. The patellar and Achilles reflexes were hyperactive. Bilateral Babinski's and Hoffmann's signs were present. Nystagmus and cranial nerve signs were absent. Roentgen studies disclosed exaggerated cervical lordosis and a mild basilar impression. A clinical diagnosis of Arnold-Chiari malformation was made.

Pneumoencephalography disclosed a filling defect in the cisterna magna. There was a tiny bubble of air in one lateral ventricle. Occipitovertebral decompression was performed. The occipitovertebral angle was abnormally acute. Surrounding the brain stem at the level of the foramen magnum was a dense band of arachnoid 4 mm. thick, that gradually shaded out in the caudad, cephalad, and lateral directions. The cerebellar tonsils were firmly plastered to the sides of the medulla, with a thin tongue extending into the foramen magnum representing an Arnold-Chiari malformation of mild degree. A separate membrane enclosed the foramen of Magendie, fused at its center with the thickened arachnoid. An incision in this membrane disclosed the dilated fourth ventricle with a deep median fissure ending in a deep calamus scriptorius. This funnel-like appearance suggested that the upper end of the central canal of the cord was patent, but gentle attempts to pass a blunt hook into it met with resistance. The 2nd cervical nerve roots pursued a normal course to their points of exit. There was no evidence of a hydromyelic sac at this level (Figs. 18 and 19).

Clinical improvement was apparent by the 4th postoperative day. Ten months after operation the patient stated that she "felt just wonderful." The hands still were numb, but they were much stronger and she was able to manage her household duties. Urinary symptoms had cleared, vaginal sensation had returned to normal, and she again experienced a normal orgasm. The biceps, triceps, and radial reflexes had returned. The patellar and Achilles reflexes still were hyperactive, and the Babinski's sign still was present bilaterally. Cutaneous sensibility was improved and she was able to recognize large objects in each hand. She wondered whether it would be all right for her to have another baby.

Comment. In this case, symptoms caused by a "syringomyelia," localized to the lower cervical region, were aggravated following surgical drainage of the sac. Subsequent progression of symptoms occurred which were benefited by dividing a band of adhesions at the level of the foramen magnum and opening the obstructed foramen of Magendie. The subsequent return of tendon reflexes in the upper extremities suggests that the sac in the lower cervical region had become smaller as the result of this operation per-

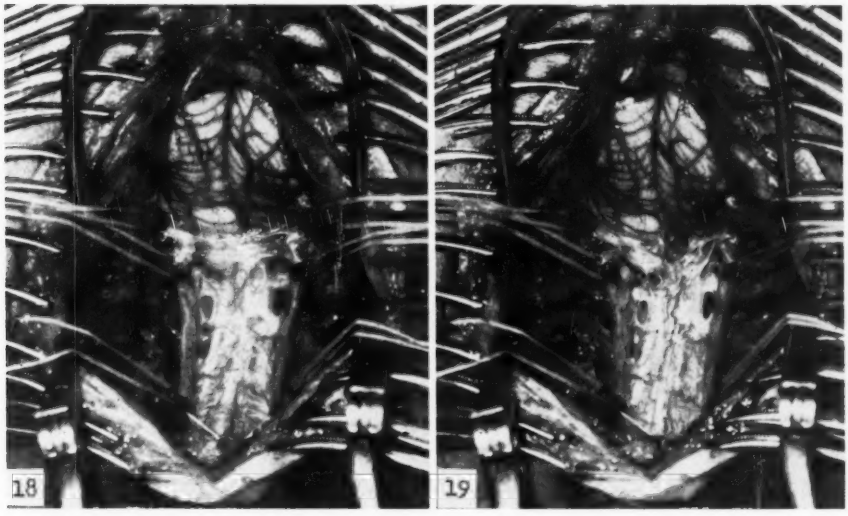


FIG. 18. Operative photograph from another case to illustrate a band of thickened meninges similar to that found in Case 3. The exposed portion of the cord is hydromyelic.

FIG. 19. Same case as in Fig. 18. After dividing the band of thickened arachnoid the tonsils were separated and a membrane occluding the foramen of Magendie was incised.

formed several segments higher. We believe, therefore, although it could not be demonstrated at operation, that the upper end of the central canal was patent, and because of the associated atresia of the foramen of Magendie, the ventricular pulse forced fluid into the patent central canal which dilated at a lower level.

Our experience suggests that a hydromyelic cyst always communicates with the fourth ventricle by a patent central canal. This is difficult to demonstrate because the upper end of the central canal, though patent, seldom is dilated. There are two reasons for this: (1) the surrounding structures are impacted in the foramen magnum, and (2) the profusion of interlacing decussating fibers at this level offers additional resistance to dilatation.

When the obstructed foramen of Magendie is surgically incised, the ventricular fluid pulse wave, instead of being funneled toward the entrance to the hydromyelic sac, is dissipated in the subarachnoid space. There its

pressure, applied externally, tends to collapse the sac. We have encountered another case in which symptoms were aggravated after incision of a "syringomyelic" cyst, and were improved after an operation similar to that described above.

DISCUSSION

Most authorities[1,2,4–6,8,13–16] on the subject of embryonal atresia of the outlets of the fourth ventricle have described a bulging membrane attached to the margins of the foramen of Magendie as its sole local expression. Upon reflection, however, it would seem that the local expression of such atresia should vary according to the physical qualities inherent in the membranes which occlude not only the foramen of Magendie but also the foramens of Luschka. The significant qualities are permeability, elasticity, and fragility. It is obvious that the less permeable the membrane, the more *severe* will be the manifestations and the earlier will they appear. The *form* of the local expression, on the other hand, depends upon the degree of elasticity in the membrane. If it is more elastic it will stretch to form a diverticulum of the fourth ventricle which may herniate through the foramen magnum (Dandy-Walker syndrome). If inelastic, the hindbrain itself will herniate (Arnold-Chiari malformation). If sufficiently fragile, it will rupture spontaneously and may thus convert an obstructive into a communicating hydrocephalus. If the occluding membrane splits into two layers, fluid may collect between them and form a cyst ("arachnoid" cyst of the cerebellum). In each of these conditions the central canal maintains its embryonal connection with the ventricular system. This is apt to result in hydromyelic distention of the central canal or, if the ependymal lining is ruptured, in the formation of a diverticulum paralleling the central canal (syringomyelia).

CONCLUSION

As encountered in the adult, certain features are common to the Arnold-Chiari malformation, to the Dandy-Walker syndrome (diverticulum of the foramen of Magendie), to cyst of the foramen of Magendie, and to syringomyelia. They are basilar impression, scoliosis, hydromyelia, a band of thickened meninges at the level of the foramen magnum, and obstruction of the outlets of the fourth ventricle by membranes, the attachments of which indicate that they are persisting remnants of the embryonic rhombic roof. Having all of these features in common it seems probable that these adult clinical entities are merely expressions of the same disease produced by a common cause, namely, failure of the outlets of the fourth ventricle to develop normally in the rhombic roof of the embryo.

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DISCUSSION*

Dr. Edgar A. Kahn: When I knew that the Department of Anatomy at the University of Michigan had embryos showing myeloschisis, I realized that here might be a chance to solve the problem of the Arnold-Chiari deformity. If one embryo could be dissected that was of an age at which differential growth between spinal cord and spine had not started, and one at an age at which the differential growth had already started, it seemed to me that Dr. Barry might work out this problem. I think that he has done a beautiful job.

The slide I am showing is of a patient with a myelomeningocele and the Arnold-Chiari deformity. We exposed the Arnold-Chiari deformity at operation, but the patient died and the entire spinal cord was dissected. You can see the slanting nerve roots, exactly as Dr. Barry showed in his specimen. There is traction close to the myelomeningocele, but no evidence of traction of the nerve roots a few segments above. The cerebellum in this case is enormous and there just is not enough room in the posterior fossa, so that I believe that the medulla has been shoved down in the cervical canal because of this, accounting for the upward direction of the cervical nerve roots.

I disagree completely with Dr. Gardner's theory, that what he is showing is the Arnold-Chiari malformation, but I'm also certain that he has a clinical condition that we should all take cognizance of. We have operated on one patient with syringomyelia at Dr. Gardner's suggestion. This patient previously had had a linear cordotomy. Though we could not demonstrate the membrane demonstrated in Dr. Gardner's cases, the clinical improvement in this patient was remarkable. I am perfectly willing, as Dr. Barry said, to call this the Gardner syndrome, but not the Arnold-Chiari deformity.

* This includes discussion of a paper presented at this meeting by Dr. Barry (see: Barry, A., Patten, B. M., and Stewart, B. H. Possible factors in the development of the Arnold-Chiari malformation. *J. Neurosurg.*, 1957, *14:* 285–301).

DR. A. EARL WALKER: Dr. Gardner and his associates have pointed out the various pathological manifestations that may occur in association with the failure of the membrane at the posterior margin of the rhombencephalon to undergo a normal dissolution forming the foramen of Magendie and the lateral foramina of Luschka. They point out that the final compensation for the congenital anomaly may be very much the same in the so-called congenital atresia of the foramina of Luschka and Magendie, the Arnold-Chiari malformations, cysts of the posterior cerebellum and in some cases of cervical syringomyelia.

I suspect that the features that these various conditions have in common are probably the result of the adjustments made by the structures of the posterior fossa to accommodate an enlarged and expanding 4th ventricle. The alterations in the posterior fossa will be modified by a number of factors, including:

(1) The age of individual at the time of failure of opening and time of progressive enlargement of the posterior fossa. In the majority of cases of congenital atresia, the anomaly develops before the third month of fetal life and, consequently, there is a failure of the occipital lobes to rotate posteriorly as they normally do, and a failure of the dural sinuses forming the lateral sinus and torcular Herophili to develop posteriorly along the occipital bone, and hence to lie in a high position in the parietal region.

(2) The degree of development that has already taken place within the cerebellum and rhombencephalon at the time of failure of the 4th ventricle to gain its natural egress to the subarachnoid space.

(3) The presence of other congenital anomalies, such as syringomyelia, that may cause alteration in the upper cervical cord, or may be present within the cerebellum itself. We have seen numerous heterotopias in such instances that would modify the compensation occurring within the posterior fossa.

In Dr. Gardner's original paper, which he gave me to read, he stated that there might be any degree of patency of the membrane over the dilated 4th ventricle. I would concur in that, for I have seen dye pass from the ventricular system to the lumbar subarachnoid space in some instances and other cases in which there was no evidence of passage of dye in this manner. This variation may be caused either by dialysis or by small fenestrations in the membrane which might occur laterally, just as they do in the septum pellucidum as a large internal hydrocephalus develops. In such cases one might expect a remission of symptoms. Indeed such often seems to be the case, for many of these patients with atresia of the foramina of Luschka and Magendie, Arnold-Chiari malformation or hydromyelia will have few, if any, symptoms during an entire life span. In fact a few instances have been reported in which the finding was simply a pathological curiosity at postmortem examination. In other cases the findings are encountered because the patient complains of headache, often initiated by trauma, with or without definite evidence of intracranial hypertension.

I suspect that in some of these cases the headaches may not necessarily be associated with the pathology that is demonstrated by the roentgenograms of the skull indicating a high position of the lateral sinus and torcular Herophili. However, there are cases such as Dr. Gardner has presented in which there is no doubt that the obstructive hydrocephalus is the result of interference with the normal passage of fluid from the 4th ventricle into the subarachnoid space. In such cases the surgical excision of the wall of the cyst and the freeing up of adhesions at the margin of the cyst may give complete relief of the symptomatology and eliminate the intracranial hypertension.

I have been particularly impressed with the association of platybasia and syringomyelia and yet have been disappointed in not a few cases at the lack of improvement following decompression of the posterior part of the 4th ventricle and cerebellar tonsils in the cervical region. Dr. Gardner's suggestion that the fluid wave being funneled towards the entrance to the hydromyelic tract may cause subsequent enlargement is an interesting hypothesis and one well worth keeping in mind. Since, if the symptoms can be relieved by directing the flow away from the opening of the hydromyelia, it is a simple matter to open up the fibers at the obex.

Finally, may I express my appreciation to the authors for this stimulating résumé of the difficult subject of congenital anomalies of the posterior part of the 4th ventricle.

DR. W. JAMES GARDNER: I want to point out, as I did to Dr. Barry personally, that there is a difference between myeloschisis and meningomyelocele. He described in his embryo an open central canal with hypertrophy of the exposed portion of the spinal cord. I cannot see how that condition can possibly go on to form a meningomyelocele. How are the meninges and the skin to bridge over a defect of the embryonic central canal of the cord when there are no structures to nourish and support these membranes? I believe that myeloschisis is a different condition from myelomeningocele.

In atresia the degree of impermeability of the persisting embryonic roof determines the severity of the symptoms and the earliness of onset. The roof may split into two layers and form a cyst. If it is inelastic, then the hindbrain is apt to herniate instead of the membrane and the result is an Arnold-Chiari malformation.

The important thing which this study has taught me is that in syringomyelia a myelogram will seldom give much information. An encephalogram, however, with a lateral view of the cisterna magna taken in a sitting position is usually diagnostic. In every patient with syringomyelia upon whom we have exposed this area, we have found obstruction of the foramen of Magendie and opening it has usually resulted in clinical improvement.

PERIARTERITIS NODOSA AS A SOURCE OF SUBARACHNOID HEMORRHAGE AND SPINAL CORD COMPRESSION

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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PERIARTERITIS nodosa has become a well recognized entity during the past 30 years. It is classified together with lupus erythematosus, rheumatoid arthritis, rheumatic fever, scleroderma and dermatomyositis in the group of collagen diseases. The following case is reported because of its unusual onset, involving subarachnoid hemorrhage and compression of the spinal cord, thus presenting an acute neurosurgical problem.

CASE REPORT

199 046. C.F., a 44-year-old white male, was admitted to the Neurosurgical Section on Aug. 25, 1955. Two weeks previously he first noted aches and pains in both thighs associated with an elevated temperature between 99°F. and 101.5°F. Within the next 2 weeks there developed in succession numbness and paresthesiae in both feet and calves, a left-sided foot drop, and paresthesiae and numbness along the C6 dermatome of the left forearm with pain in both shoulders. On the day prior to admission the patient experienced severe pain in the lower thoracic spine followed by a sudden motor, sensory and sphincteric paralysis with a level below the T9 cord segment. Lumbar puncture performed at another hospital revealed grossly bloody spinal fluid with an initial pressure of 280 mm. of water, as well as a spinal-fluid block. The history further revealed that bronchial asthma had developed 10 months before admission and that the patient was found to be sensitive to feathers, coffee, tea, cold foods, spinach and alcohol.

Examination. Blood pressure was 134/80, pulse rate 86, and temperature 101.2°F. General physical findings were normal. There was a complete motor, sensory and sphincteric paralysis with a level at the T9 cord segment, weakness in the biceps and triceps, and hypalgesia in the C6 dermatome on the left. There was no nuchal rigidity and the cranial nerves were normal.

The blood count was normal except for a white blood count of 16,200 with 78 per cent neutrophils. The urine was normal except for a trace of albumin and 1-plus glycosuria.

Emergency lumbar and cisternal myelograms revealed complete blocks at L2 and C2 respectively. The spinal fluid was grossly bloody with a total protein of 5.1 gm.

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Operation. Laminectomy of T6–T9 was carried out on the day of admission with a preoperative diagnosis of thrombosed and ruptured varicosities. The intradural exploration revealed a solid mass of recent blood clot throughout the entire extent of the operative field; thrombosed worm-like vessels were seen and felt in the center of the exposure. Following a wide decompression the wound was closed.

Course. Throughout the immediate postoperative period the patient continued to run a temperature of 100°F.–103°F., and the neurological status remained unchanged. On Sept. 7, 1955 examination of the urine revealed 3-plus albuminuria with pyuria, hematuria and cylindruria. On Oct. 4, 1955 hemoglobin was 8.9 gm.; there were 17,000 white blood cells with 31 per cent eosinophils. This pattern continued until death, with the eosinophils varying between 19 per cent and 41 per cent. The patient was treated empirically with Gantrisin, penicillin, Terramycin and Achromycin without effect. Paralysis of the left diaphragm with pneumonitis at the left base occurred on Oct. 10, 1955. On Nov. 4, 1955 the patient complained of weakness in the right upper extremity, and paralysis of the intrinsic muscles of the hand was noted.

Because of the persistent fever, leukocytosis, eosinophilia, anemia, albuminuria, and the 10 months' history of bronchial asthma, periarteritis nodosa was suspected. Two muscle biopsies were negative, although one showed acute and chronic myositis. Several lupus erythematosus preparations were negative. Aspiration of bone marrow revealed a marked eosinophilia. Serum electrophoresis showed decreased albumin with normal globulin. Brucellosis agglutinins, Coomb's test, cryoglobulins and trichinosis complement fixation tests were all negative.

On Dec. 26, 1955, bulbar speech with weakness of the right lower facial muscles, the right masseter muscle and right palate was noted, as well as deviation of the tongue to the right. On Dec. 27, 1955, the patient complained of diplopia on right lateral gaze. At this time blood pressure was 160/95, and pulse rate 127. Hemoglobin was 10 gm.; there were 3.3 million red blood cells, 18,000 white blood cells with 24 per cent eosinophils, 16,500 platelets, 0.3 per cent reticulocytes, and blood urea nitrogen was 17.

On Jan. 3, 1956 the patient showed nuchal rigidity and petechiae were found on his back and chest. A Jacksonian seizure involving the left upper extremity occurred on Jan. 5, 1956. Examination revealed bilateral lower facial and palatal weakness with absent pharyngeal reflexes. Cortisone therapy was started on this date. Cheyne-Stokes respiration and difficulty in swallowing were noted on Jan. 14, 1956. There then developed a left medial rectus palsy, deafness on the right, and nystagmus on left lateral gaze. Bilateral nystagmus was present on Jan. 15, 1956 with marked impairment in left visual acuity. On Jan. 17, 1956 Cheyne-Stokes respiration recurred and the patient expired.

Autopsy. The body showed marked wasting. There was a large decubitus ulcer in the right gluteal region. There were approximately 300 cc. of yellow purulent fluid in the left pleural cavity. The vessels in the mesentery of the small bowel were hard and nodular. There were hemorrhagic spots and two large ulcerations in the gastric mucosa. There was a large ulcer in the rectal mucosa near the anus. The subcapsular surfaces of the kidneys were nodular and mottled by areas of light yellow-brown discoloration. The mucosa of the urinary bladder was severely congested. The testes were atrophied.

Microscopically there was lymphocytic infiltration into the subepicardium and hepatic parenchyma. The arterioles and smaller arteries in the heart, lungs, gastro-

intestinal tract, liver, gallbladder, spleen, pancreas, adrenals, muscle, skin, lymph nodes, kidneys and bladder showed a similar pattern, consisting of fibrous thickening of all layers, perivascular lymphocytic infiltration and occasional fresh and organized thrombi. The thickened intima showed hyaline necrosis and the lumina were greatly narrowed. There were no pathological changes in the peripheral nerves.

The brain weighed 1580 gm. The leptomeninges showed recent, small hemorrhages in the right Sylvian fissure, cisterna magna and cisterna ambiens. Section of the cerebrum revealed a sharply defined recent hemorrhage in the left caudate nucleus, internal capsule and putamen which had ruptured through the head of the caudate nucleus into the left lateral ventricle. There was a smaller recent hemorrhage into the lateral aspect of the right thalamus. The third and largest hemorrhage was present in the central white matter of the left inferior temporal gyrus and extended back into the left occipital lobe. A fourth, apparently older hemorrhage, was found in the right inferior occipital gyrus. Section of the cerebellum and brain stem revealed no gross lesions. The left temporal cortex was studded with a series of perivascular hemorrhages.

Microscopically a number of venules showed polymorphonuclear infiltration of their walls and of the parenchyma about them; one was thrombosed. The walls of the leptomeningeal vessels showed marked changes. The layering was no longer discernible. The walls were fibrosed and the lumina were occluded. The thrombus material was necrotic and partially organized. There were lymphocytes and hemosiderin-laden phagocytes and plasma cells in the outer portions of the walls. The cortex in this area had undergone extensive degeneration with loss of cortical architecture; only amorphous, pink material containing masses of lemon-yellow pigment and cellular debris was present. In the upper midbrain a leptomeningeal artery showed fibrinoid necrosis of its wall, occlusion of its lumen, considerable polymorphonuclear infiltration and proliferation of mesenchymal elements. There were scattered perivascular hemorrhages in the pons, medulla and cerebellum.

The thoracic cord was soft to palpation. Section through the cervical cord revealed a homogeneous white discoloration of the column of Goll. The architectural markings of the mid-thoracic cord and area caudal to this were obscure. In the region of the operation the cord was reduced to a spongy dark brown collapsed band in which no remnants of normal tissue could be detected. There was a recent hemorrhage into the thoracic leptomeninges, and a small artery in this region showed infiltration of its wall by lymphocytes and polymorphonuclear leukocytes. A small leptomeningeal artery showed fibrinoid necrosis of its wall, narrowing of its lumen and marked polymorphonuclear infiltration and proliferation of mesenchymal cells in the adventitia (Fig. 1). Similar but less intense changes were found in the cervical region. There was degeneration of the central posterior columns in the thoracic region. There were fresh petechiae in the gray matter. Degenerated myelin sheaths and phagocytes were found in the columns of Goll and the spinocerebellar and spinothalamic tracts in the cervical region.

DISCUSSION

Miller[21] defined periarteritis nodosa as "a form of necrotizing inflammatory panarteritis affecting small and medium-sized arteries, accompanied both by signs of systemic infection and by focal symptoms due to the scattered primary arterial lesions and to the local circulatory disturbances varying from relative ischemia to gross infarction. . . ."

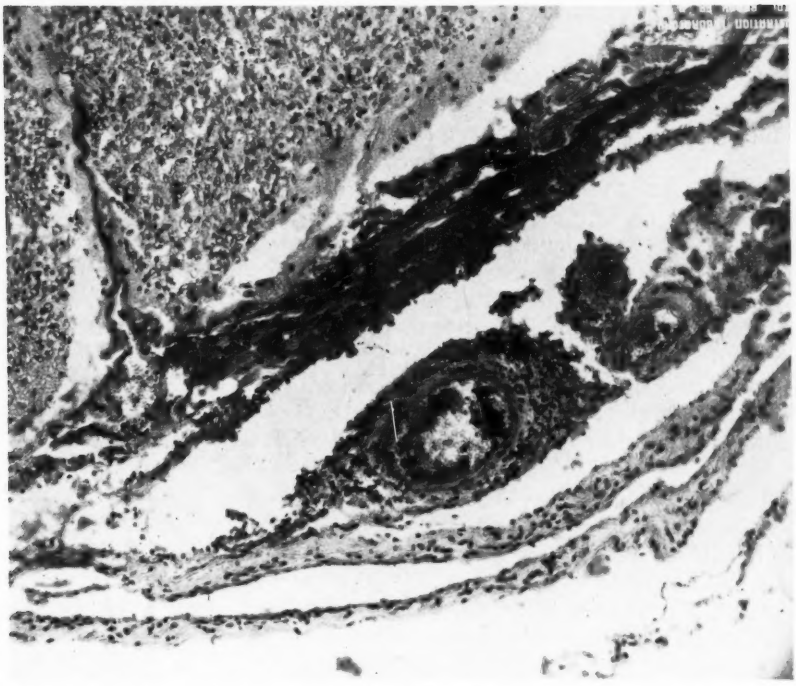

FIG. 1. A small thoracic leptomeningeal artery showing fibrinoid necrosis of its wall, narrowing of its lumen and marked infiltration of polymorphonuclear cells in the adventitia. (×115)

Matani first described nodules along smaller arteries in 1755 and aneurysms were described by von Rokitansky in 1852. Kussmaul and Maier were credited with describing the syndrome of periarteritis nodosa in 1866. Ferrari in 1903 suggested the term "polyarteritis nodosa" since he found involvement of all coats of the artery.[19]

In addition to the terms periarteritis and polyarteritis, necrotizing angiitis,[12] disseminated necrotizing panarteritis,[31] and maladie de Kussmaul have been used.[26] Zeek[32] favored the term "necrotizing angiitis" for the group consisting of periarteritis nodosa, hypersensitivity angiitis, rheumatic arteritis, allergic granulomatous angiitis, and temporal or cranial arteritis. In hypersensitive angiitis the smallest branches of blood vessels are involved and the walls are infiltrated with eosinophils. The heart is involved primarily in rheumatic arteritis. Granulomatous lesions have been found in patients with bronchial asthma by Newman and Wolf,[23] distinguishing allergic granulomatous arteritis from periarteritis. Temporal arteritis is considered part of periarteritis, and but a local manifestation of a widespread arteritis.[7,21] However, differences in involvement of vessels, age, sex and prognosis have been noted.[11]

The etiology for periarteritis remains obscure. That it is said to be caused by "chronic recurrent urticaria of blood vessels"[21] indicates how favorably the theory of anaphylactic hypersensitivity is considered, with the arterial system serving as the organ of shock. Rich and Gregory[25] have produced lesions typical of periarteritis by injecting foreign serum and sulfa drugs into rabbits. Arkin[1] felt that periarteritis was a form of postinfectious mesarteritis. Lues, streptococci, sulfa, arsenicals, iodine and thiourea have also been considered.[10] However, Griffith and Vural[9] found no evidence of sulfa as a factor and challenged the theory of hypersensitivity.

Griffith and Vural[9] found an incidence of only .083 per cent in postmortem material over a period of 10 years. In 1926, only 70 cases of periarteritis had been reported; in 1939, there were 395 cases in the literature.[32] Males outnumber females 3–4 to 1,[7,9,19] although Hagans[10] reported an equal sex incidence. Age varies from 10 days to 77 years, with most cases occurring between 20–50 years.[9,19] In 9 per cent of all cases the disease has been found in children. Baló[2] has reported periarteritis in pigs, dogs, deer and calves.

Clinically, periarteritis is a nonspecific, subacute or chronic pyrexial illness, characterized largely by atypical abdominal ileus, primary renal disease, and a combination of polyneuritic and polymyositic manifestations. Typical of the disease is the polymorphic and changing character of the symptoms. In an analysis of 300 cases,[12] fever was found in 85 per cent, abdominal pain in 65 per cent, hypertension in 60 per cent, edema and neuritis in 50 per cent, weakness and loss of weight in 45 per cent, cough, dyspnea, vomiting and headaches in 30 per cent, precordial pain in 25 per cent, and jaundice, convulsions, eruptions of the skin, diarrhea and soreness of muscles in 10 per cent of the cases. A history of allergy was found in 21 per cent.[17] There was leukocytosis in 80 per cent, albuminuria in 60 per cent, hematuria in 40 per cent, eosinophilia in 25 per cent, and uremia in 15 per cent.[12] In over 50 per cent of the cases there was sudden onset of fever. Other symptoms include pallor, tachycardia, malaise, anorexia, cachexia, ulcers of the mouth, palpable subcutaneous nodules and localized subcutaneous edema. Hypertension and fever are a significant combination. Any asthmatic patient with marked eosinophilia should be suspected of harboring periarteritis nodosa. The presence of Rackemann's triad consisting of asthma, numbness in the extremities and an eosinophilia over 25 per cent indicates periarteritis with a poor prognosis.[24] The diagnosis is usually confirmed by muscle biopsy, but negative biopsies are common in proven cases.[10,32] Periarteritis can be mistaken for trichinosis, myositis, purpura hemorrhagica, typhoid, amebiasis, liver abscess, miliary tuberculosis, meningitis, brain tumor, alcoholic polyneuritis and lead neuritis.[16]

The central nervous system is involved in 8 per cent of the cases according to Arkin,[1] and in 20 per cent according to Logue and Mullins,[17] and Malamud and Foster.[20] In 65 patients with involvement of the central nervous system out of 300 patients with periarteritis, the latter authors

found 24 with convulsions, 14 with meningeal irritation, 14 with organic brain syndrome, 11 with hemiplegia and sluggish light reflexes, 10 with anisocoria, 4 with bloody spinal fluid, and 1 with transverse myelitis. Other conditions mentioned include chorea, pseudobulbar palsy, decerebrate rigidity, cranial nerve palsy, diabetes insipidus, vertigo, thrombosis of central retinal artery with retinal detachment,[16] and Hunt's syndrome.[29] Isolated involvement of the central nervous system is apparently rare. Despite widespread pathological involvement, symptoms and signs usually make a late appearance. In order, the 7th, 9th, 10th, 5th, 3rd, 4th and 12th cranial nerves are commonly involved.[30]

Arkin[1] reported involvement of the peripheral nervous system in 20 per cent, Boyd[4] in 33 per cent, Heathfield and Williams[13] in 40 per cent, and Lovshin and Kernohan[18] in 52 per cent of patients. Neuritis usually occurred within 4 months of the onset of the disease. Pain in the calves is usually the first sign of polyneuritis. The most suggestive feature of polyneuritis is its variable behavior. It may begin abruptly or slowly, and may develop in a single or all extremities. Multiple neuritis usually occurs asymmetrically, and separate nerves are involved in succession (mononeuritis multiplex) which, according to Kernohan and Woltman,[16] is a rather characteristic feature of periarteritis nodosa. There may also be symmetrical involvement of peripheral nerves; some authors found this more common than mononeuritis multiplex.[13,21] Upper and lower extremities are involved equally. Distal paralysis is more common and severe. Sensory involvement is less marked than motor loss, with vibratory and position senses impaired more often than other modalities. Symptoms consist of pain, paresthesia, anesthesia, tenderness of nerves and muscles, paralysis, decreased deep tendon reflexes and atrophy. The pain is described as "shooting and burning," and is worse at night. Extensors of the feet are affected more than flexors. The brachial plexus and sciatic and femoral nerves are most commonly involved. Periarteritis nodosa is the third most frequent cause of peripheral neuropathy, following diabetes mellitus and acute infectious polyneuritis.[13]

A recent analysis of causes of bleeding into the subarachnoid space failed to mention periarteritis.[22] However, Malamud and Foster[20] have reported a 5 per cent incidence of subarachnoid hemorrhage in 300 cases of periarteritis. There have been numerous reports of hemorrhage with lesions in the brain stem, cerebral cortex and spinal cord. Aneurysms with rupture have been reported.[5,26,29] However, despite the fact that the name periarteritis nodosa denotes gross aneurysmal dilatation of the arteries, aneurysms are rarely found. "Massive brain hemorrhages in polyarteritis nodosa may, from a theoretical point of view, be expected to occur as easily as hemorrhages from diseased arteries in other organs. The reason for the exceptional rarity of such an event is obviously the fact that polyarteritis in the brain is relatively infrequent and then affects predominantly the pial arteries."[14] It is felt, then, that in most cases of subarachnoid hemorrhage in periarteritis nodosa the cause is not aneurysmal dilatation and rupture but ruptured

panarteritic vessels. Thrombocytopenia is mentioned as a cause of subarachnoid hemorrhage in a patient with lupus erythematosus;[28] this may have been a factor in our case. Boyd[5] raised the question of periarteritis nodosa in idiopathic subarachnoid hemorrhage.

Transverse myelitis is reported as occurring in only 2 per cent of cases by Malamud and Foster.[20] Severe myelomalacia, degeneration of anterior and lateral columns, and thrombosis of spinal arteries have been described.[4,26] Landry's ascending paralysis has been reported by Baló.[2] Similar lesions have been seen in lupus erythematosus.[28]

The primary lesion is a hyaline-like necrosis of the media and internal elastic lamina.[16] This fibrinoid necrosis is a nonspecific response of connective tissue to injury, and is caused by precipitation of acid mucopolysaccharides in ground substance.[12] Banks[3] noted this fibrinoid change as a common denominator in periarteritis nodosa, lupus erythematosus, rheumatoid arthritis, rheumatic fever, scleroderma and dermatomyositis. Arkin[1] has found lesions in the kidney in 80 per cent of cases, heart 70 per cent, liver 65 per cent, gastrointestinal tract 50 per cent, mesenteric artery 30 per cent, muscle 30 per cent, pancreas 25 per cent, peripheral nerves 20 per cent, and in the central nervous system in 8 per cent. Arteries of 3–4 mm. diameter are involved; veins are only rarely involved. Arkin divided the changes into four stages: degeneration, inflammation, granulation, and healing. In the first stage there are hyaline degeneration and edema in the media. Inflammatory cells then infiltrate this area. Similar changes occur in the adventitia and intima. The lesions are usually elliptical, with the greatest diameter parallel to the long axis of the vessel, and often less than 1 mm. in diameter. During the granulation stage thrombosis or aneurysms may occur. In the healing stage a scar is formed and nodules may be formed because of extension of healing beyond the confines of the vessel; these occur in 23 per cent of patients. Lesions consisting of all four stages can be found simultaneously. Final evolution of vascular changes may result in intimal proliferation with thrombosis, aneurysmal dilatation and nodules. Thrombosis leads to infarction, and aneurysms predispose to hemorrhage. Hiller[14] favored the interference with the blood supply to the brain as the cause of lesions and cerebral symptoms; however, Kernohan and Woltman[16] favored anoxemia or a toxin rather than inadequate blood supply as the explanation.

Although Rose *et al.*[27] reported a 5–10 per cent and Grant[8] a 50 per cent spontaneous cure, the mortality is usually listed as 80–90 per cent. In 50 per cent of the cases there have been remissions of several years' duration.[7] Death usually occurs within 2 years of onset of symptoms, averaging 6–12 months.[9,10] Those with renal lesions, involvement of the central nervous system, and Rackemann's triad have a poorer prognosis.[7,24]

Therapeutically there is little to offer except symptomatic therapy. Glaser[7] has found that ACTH reduces the fever in 1 to 5 days and decreases pain and swelling in the joints in 7 days. However, the effects of anemia, leukocytosis and hypertension are variable.[6] Therapy may lead to com-

plications and is ineffectual in patients with renal and central nervous system symptoms. Surgery has been used for hypertension.[15] In addition to the steroids, salicylates, Atabrine, nitrogen mustard, TEM and PABA have been tried without success. The general attitude is that steroids are of doubtful help but should at least be tried.

SUMMARY AND CONCLUSIONS

1. A case of periarteritis nodosa with widespread involvement of the central nervous system is reported. The patient, a 44-year-old white male, presented initially an acute neurosurgical emergency in view of the sudden onset of pain in the lower thoracic spine with paraplegia, and the subsequent findings of spinal fluid block and subarachnoid hemorrhage.

2. In the beginning, the operative exposure of what appeared to be thrombosed spinal varicosities within a subarachnoid hematoma seemed to offer an acceptable explanation for the symptoms.

3. However, the history of bronchial asthma, polyneuritic and polymyositic symptoms, the febrile course with the later findings of albuminuria, hypertension, eosinophilia, anemia and leukocytosis as well as the spread and extension of the neurological manifestations appeared to support the presumptive diagnosis of periarteritis nodosa.

4. Although muscle biopsies were not diagnostic, the autopsy revealed generalized vascular and perivascular changes typical of periarteritis nodosa, with lesions in all organs, especially the central nervous system. Aneurysmal dilatations of the affected blood vessels were not found.

5. In the differential diagnosis of idiopathic subarachnoid hemorrhage, particularly in the presence of fever and polymorphic symptoms, periarteritis nodosa should be considered.

6. Involvement of the central nervous system by periarteritis nodosa has been observed in 8–20 per cent of the cases. Transverse myelitis occurs rather infrequently as compared to cerebral lesions.

7. A review of the literature is presented with a discussion of the pathological, etiological and therapeutic aspects of periarteritis nodosa.

The authors would like to thank Dr. Erich G. Krueger for his guidance and criticism.

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STUDIES OF TRIGEMINAL NERVE POTENTIALS

OVERREACTION TO TACTILE FACIAL STIMULATION IN ACUTE LABORATORY PREPARATIONS*

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EVOKED trigeminal nerve potentials in normal cats and monkeys have been reported.[3] Alterations of trigeminal nerve potentials associated with chronic overreaction to tactile facial stimulation in cats have also been described.[4] However, these chronic animals took 3 to 4 months to prepare and large numbers of animals were required in order to obtain a significant number of good preparations for subsequent recordings.

A new preparation therefore seemed desirable in which during the course of an acute experiment overreaction to tactile facial stimulation could be produced and simultaneous records could be obtained of evoked trigeminal nerve potentials. This report describes electrophysiologic recordings of trigeminal nerve potentials from 60 cats in which overreaction to tactile facial stimulation was produced during the course of acute experiments.

TECHNIQUE

Adult cats weighing 2–4 kg. were anesthetized with 12.5 to 37.5 mg. of thiamylal sodium (Surital) given intrathoracically and endotracheal ether. The medulla and upper cervical cord were exposed. The posterior root, gasserian ganglion, and peripheral divisions of the trigeminal nerve were exposed in the middle fossa. A segment of the infraorbital nerve was then exposed. Anesthesia was discontinued after the surgical preparation.

Recordings were begun 1 to 1½ hrs. after ether anesthesia was discontinued. The animals were responsive to stimulation but lay quietly on the supporting table. Rectal temperatures remained normal during recording periods. Succinylcholine chloride (Anectine) was not used as in earlier studies since exaggerated facial and body movement in response to light stroking or touching of facial fur were the primary indices of overreaction.

Bipolar steel needle electrodes with uninsulated tips (60 to 80 μ) 1 to 2 mm. apart were inserted into the 2nd division of the trigeminal nerve in the middle fossa. Nichrome wire bipolar electrodes with exposed tips up to 60 μ and offset 1 mm. from each other were inserted into spinal V caudal to the obex of the 4th ventricle with a micromanipulator. Recordings from these electrodes were obtained on a dual beam oscilloscope with coupled amplifiers of conventional capacity.

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Stimulating electrodes were placed on the infraorbital nerve. Monophasic stimuli (Grass stimulator Model No. S4C) of 0.01 msec. duration were raised from threshold voltage to that voltage required to evoke a maximum afferent response in the 2nd division of the trigeminal nerve in the middle fossa. The stimulus required to evoke a maximum response was used in these studies unless otherwise indicated.

Overreaction to tactile facial stimulation was produced by applying strychnine or thio-carbohydrazide over the surface of spinal V, 1 to 3 mm. caudal to the obex of the 4th ventricle. Strychnine dilutions of 1 per cent and 5 per cent were effective but a tiny crystal of strychnine under a 2 mm. pledget of cottonoid gave prompt and lasting results. It could be readily removed by irrigation.

The overreaction to tactile and electrical stimulation was graded + to ++++ during the protocol. Cursory efforts were made to record this overreaction using electrodes in the upper and lower eyelids, the tip of the ear, and in the interscapular region. These electrodes were led to a 4-channel Grass electroencephalographic machine (Model No. III D) for recording of movement and muscle activity.

RESULTS

Since Anectine could not be used in this study (movement being the primary index to overreaction) it was necessary to exclude any artifact caused by movement or muscular contractions which might be recorded directly or by remote pickup in the recording nerve electrode (Fig. 1). Monitor electrodes were therefore inserted into the temporalis muscle, cervical paraspinal muscles, forehead, cheek, and chin muscles, cervical strap muscles, periosteum at the foramen rotundum, petrous ridge and sphenoid wing, and into the hippocampus and cerebral peduncle. From

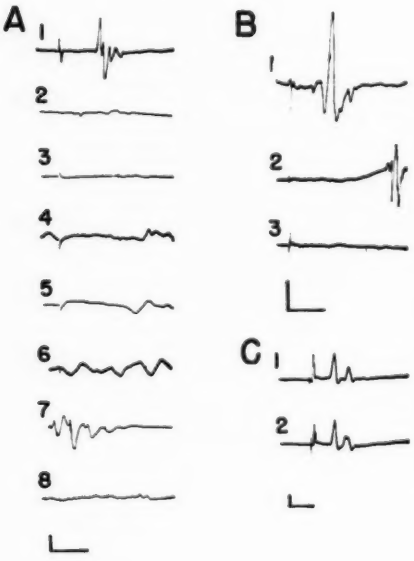


FIG. 1. (A) Recording obtained from electrodes placed in the 2nd division of the trigeminal nerve in the middle fossa (1), cervical paraspinal muscles (2), facial muscles of forehead (3), and chin (4), periosteum of the petrous ridge (5) and foramen rotundum (6), cervical strap muscles (7), and hippocampus (8).

(B) Recordings from 2nd trigeminal divisions in the middle fossa (1), temporalis muscle (2) and cerebral peduncle (3).

(C) Recordings from 2nd division of the trigeminal in the middle fossa before (1) and after (2) section of all the motor cranial nerve outflow on the ipsilateral side from the 3rd, 4th, motor 5th (with the 3rd division), 7th, and lower cranial nerves inferiorly to include the motor roots of the upper cervical segments. Stimuli in each instance were delivered to the infraorbital nerve. Calibration indices are for 250 μV. and 5 msec. in this and each succeeding illustration unless otherwise stated.

none of these regions could we record potentials similar to those in the 2nd division of the trigeminal nerve in the middle fossa. Those monitor electrodes placed so as to record movement showed no change in the base line until 20 or more msec. after the stimulus, which was later than the termination of the most prolonged evoked trigeminal potential. The monitor electrodes in the temporalis muscle showed muscle potentials beginning 20 to 30 msec. after the stimulus. All of the other muscle potentials recorded had an even longer delay. The monitor electrodes in the periosteum of the foramen rotundum, petrous ridge, sphenoid wing, hippocampus and cerebral peduncle maintained a flat base line following stimulation and gave no evidence of remote pickup of potentials from the trigeminal nerve or more remote structures.

A second system of control was employed. While recording potentials from the 2nd division of the trigeminal nerve in the middle fossa, all motor cranial nerves on the ipsilateral side of the head were severed serially and the 2nd and 3rd cervical motor roots were cut. No change in the evoked trigeminal potentials followed these procedures. Eleven animals were studied during these control studies and no interference from remote pickup, movement, or muscle potentials could be identified.

These observations differ from those previously described[3,4] using Anectine and anesthesia. The afferent spike and the stimulus required for threshold and maximum responses remained the same. However, the amplitude of the delayed activity was increased in voltage from three to six times over records taken under Surital anesthesia with Anectine and artificial respiration.

Surital in the usual dosage and artifical respiration alone did not change the characteristics of the delayed activity. Small intravenous doses of Anectine, however, caused a marked reduction of this potential. Following Anectine (1.0 mg.) there was only slight evidence of weakness and no alteration in respiration or responsiveness. The delayed activity, however, might be reduced to almost a flat base line and remain there for several minutes (Fig. 2).

When a tiny crystal of strychnine was applied to the surface of the medulla over the caudal portion of spinal V a characteristic sequence of events followed. Within 1 min. light stroking of fur in the distribution of the ipsilateral 1st trigeminal division caused a quick blink, squint, and flattening of the pinna and a quick movement of the ipsilateral shoulder and forepaw. Within $1\frac{1}{2}$ to 3 min. stroking fur in the region of the 2nd trigeminal division was also associated with marked overreaction, and within 2 to 4 min. a similar response was elicited by stroking or touching fur in all three divisions of the trigeminal. This state of overreaction to tactile facial stimulation persisted as long as the strychnine remained in place (up to 2 hrs.) or for 20 to 30 min. after removal of the strychnine. Occasionally stroking the pinna and fur of the neck caused overreaction. Spread of the overreaction to adjacent dermatomes and spinal seizures rarely occurred during recording

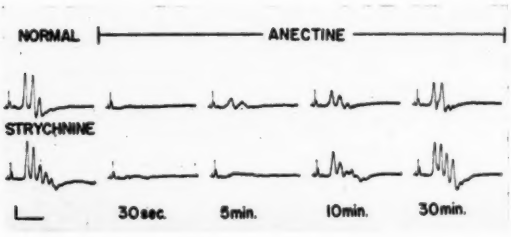


FIG. 2. Anectine markedly suppressed the centrifugally conducted delayed activity, as indicated in the text. The upper line of records were obtained before applying strychnine to spinal V. The lower records were obtained after applying strychnine to spinal V. In each instance 1.0 mg. of Anectine was given intravenously. Overreaction became marked after the application of strychnine and disappeared after the subsequent injection of Anectine. There was slight return of overreaction to tactile facial stimulation 10 min. after the Anectine and it was again marked at 30 min. Fifty min. intervened between the two doses of Anectine. There was no apparent change in respiration or in the animal's movements in response to painful stimuli following either injection of Anectine.

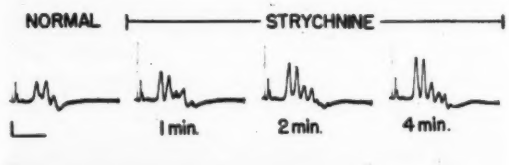
periods and appeared to be correlated with diffusion of strychnine by cerebrospinal fluid or serum coming into contact with the cottonoid pledget.

The trigeminal nerve potentials recorded during the 5 min. when the overreaction was becoming maximal after strychninization increased the delayed activity both in amplitude and duration (Fig. 3). Delayed activity consisted of as many as seven or eight major waves, compared with only three or four crests seen without strychnine.

In three preparations stimulation of the infraorbital nerve evoked a delayed potential in the dorsal root of C2. In one instance a similar delayed potential was recorded in the 2nd division of the trigeminal after stimulation of C2 dorsal rootlets. A close anatomic association between the trigeminal and the high cervical sensory roots has been well established[2] and will be further studied with these techniques.

If in addition to submaximal electrical stimulation of the infraorbital nerve (at frequencies of 1 per sec.) the fur over the eyebrow or cheek was gently stroked, the delayed activity recorded in the 2nd division increased in voltage and complexity as long as the stroking was continued (Fig. 4).

FIG. 3. These records were obtained with recording electrodes in the 2nd division of the trigeminal in the middle fossa and a stimulus applied to the infraorbital nerve. The delayed activity clearly increases in amplitude in all of its component parts and is prolonged by the appearance of at least three additional wave forms. Overreaction to tactile facial stimulation was minimal 1 min. after the application of strychnine and maximum at 4 min.



This augmentation of the evoked delayed potential by the addition of unsynchronized afferent impulses from cutaneous touch endings has been seen repeatedly in overreactive preparations but not in normal preparations. Light touch stimuli applied to whiskers of the upper lip with a wand (with a 1-cm. excursion) are also effective in evoking this delayed activity (Fig. 5).

The increased delayed activity and the associated overreaction were abolished by small intravenous doses of several drugs. Anectine (1.0 mg.) reduced even the delayed activity in strychnine preparations to a flat base line (Fig. 2).* Veratrine (0.25 mg.), decamethonium bromide (Syncurine) (0.2 mg.), mephenesin (Tolserol)† (Fig. 6), ether (20 to 30 sec. after introduction into the airway) and diphenylhydantoin sodium (Dilantin) (50 mg.) had a similar effect. Chlorpromazine

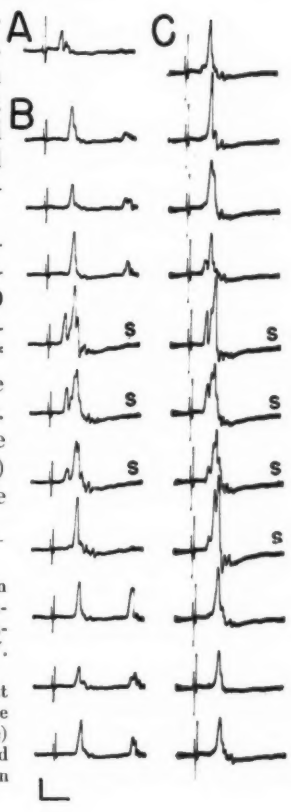


FIG. 4. (A) This record was obtained in the usual manner from the 2nd division of the trigeminal nerve while stimulating the infraorbital nerve. Stimulation in this illustration was 0.01 msec. in duration at 6 V. Threshold for an afferent spike was approximately 1.5 V. Maximum afferent spike could be evoked at 20 V.

(B and C) With the addition of strychnine and taking records at 1-sec. intervals the additional stroking of fur over the eyebrow in the 1st trigeminal division (indicated by "S" on each appropriate frame) was always accompanied by a marked increase in the amplitude and duration of the delayed activity evoked by submaximal stimulation of the 2nd division.

hydrochloride (Thorazine) (50 mg.), zoxazolamine, 2-amino-5-chlorobenzoxazole (Flexin) (5 mg.), azacyclonol (Frenquel) (25 mg.) did not change the evoked potentials or overreaction. Clamping the tracheal cannula reduced the delayed potential and overreaction after a 2-min. period of anoxia.

Compression of the semilunar ganglion or posterior root abolished the delayed activity recorded in the 2nd division (distal to the region of trauma) and simultaneously stopped the overreaction to tactile facial stimulation. In association with this trauma there was no reduction in evoked cortical potentials and no clinically demonstrable hypesthesia (Fig. 7). Evoked responses in spinal V were usually diminished after the compression (Fig. 8). The afferent spike and delayed activity in the posterior root (proximal to the region of injury) may also be diminished to a major degree, but less than

* Succinylcholine has also been found to block cardiac synapses.[6]

† The mephenesin (Tolserol) used in these studies was graciously supplied by E. R. Squibb & Sons, New York.

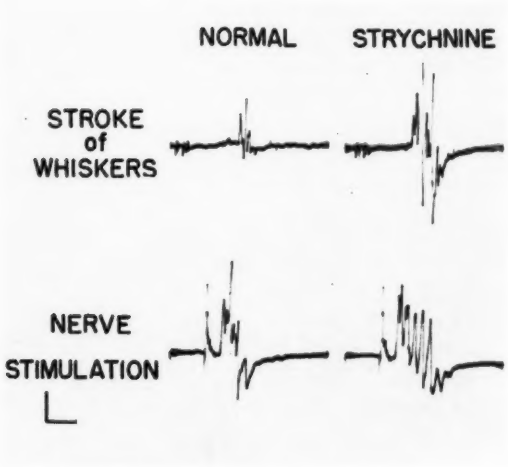
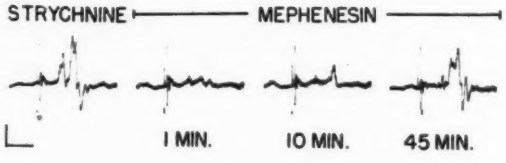


FIG. 5. The upper two frames record potentials evoked in the 2nd division in response to tactile stimulation of whiskers in the 2nd division before and after strychnine. The lower two frames demonstrate the response to electrical stimulation of a portion of the infraorbital nerve before and after strychnine. The apparent prolonged delay in the upper recordings was caused by mechanical lag in the wand which was activated by induction coils and had a 1-cm. excursion.

FIG. 6. This recording from the 2nd division of the trigeminal nerve followed stimulation of the infraorbital nerve. The 1st and 3rd divisions were previously sectioned. Strychnine was applied over spinal V and overreaction was recorded as ++++. Mephenesin (100 mg.) was then given intravenously. Within 1 min. the delayed activity was markedly reduced and overreaction was absent. Ten min. later the delayed activity was again increasing. Minimal overreaction was evident at approximately 25 min., and was noted to be +++ at 45 min. when the delayed activity became nearly maximal.



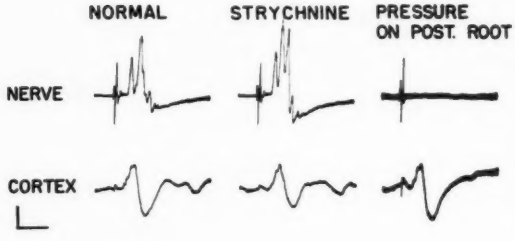


FIG. 7. Recordings from the 2nd division of the trigeminal in the middle fossa and from the contralateral primary sensory cortex. Stimuli delivered to the infraorbital nerve. Following strychnine applied to spinal V there is no change in the evoked cortical potential whereas there is a clear increase in amplitude and duration of delayed activity in the 2nd division. Following mild trauma to the posterior root the evoked cortical potential remains unchanged although the delayed activity is absent, although the strychnine remained in place. Overreaction to tactile facial stimulation, which developed after the application of strychnine, was absent from all three trigeminal divisions following compression of the posterior root.

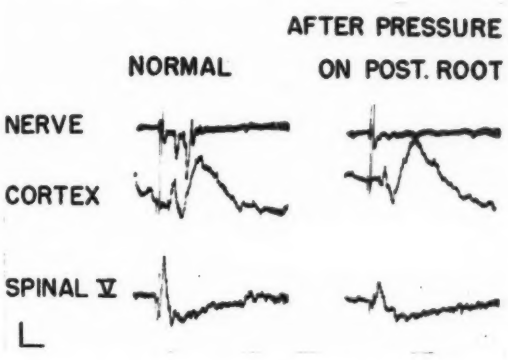


FIG. 8. The recording system was similar to that of Fig. 7. After compression of the posterior root the evoked response in spinal V was diminished although the evoked cortical response was not changed. Delayed activity in the 2nd division was also markedly diminished, and overreaction to tactile facial stimulation was absent.

the delayed activity in the 2nd division distal to the trauma. During the effective period following trauma a stimulus applied to spinal V could evoke delayed activity of high voltage in both the posterior root and (after minimal trauma) in the 2nd division distal to the site of compression. No associated overreaction was evident unless delayed activity of high voltage was recorded in the 2nd division distal to the trauma.

These findings following trauma to the gasserian ganglion suggested that conduction of the delayed activity to the peripheral components of the trigeminal nerve might be a prerequisite to the animal showing overreaction. Therefore the peripheral divisions of the trigeminal nerve were severed distal to the stimulating and recording electrodes. The 1st and 3rd divisions were severed in the middle fossa and the 2nd division was cut distal to the stimulating electrodes on the infraorbital nerve. The cutaneous end-organs were thereby denervated. Section of each successive division

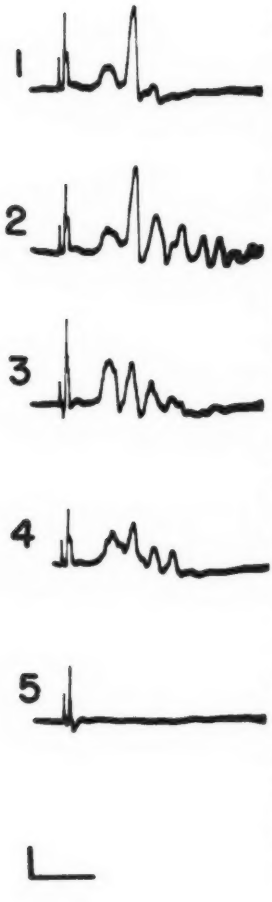


FIG. 9. These serial records evoked in the 2nd division of the trigeminal in the middle fossa by stimulating a portion of the infraorbital nerve were obtained: (1) as a normal control; (2) following strychnine to spinal V; (3) after sectioning the 1st and 3rd (and motor) trigeminal divisions in the middle fossa; (4) after division of the remaining portions of the 2nd division distal to the stimulating electrode; and (5) after division of the posterior root. Overreaction was marked following application of strychnine and persisted in response to nerve stimulation until all three divisions were cut and the skin was completely denervated. The overreaction to nerve stimulation diminished somewhat after each successive sectioning of a division of the trigeminal nerve.

of the trigeminal in this manner reduced the amplitude of the delayed potential in the 2nd division (Fig. 9). The remaining potential could then be abolished by section of the posterior root. Prior to division of the posterior root the animal could lick and blink spontaneously. There was no exaggeration of facial movements associated with stimulation of the 2nd division. There was no overreaction to stimulation of spinal V so long as all three divisions of the trigeminal nerve were completely severed. Frequently a small area of skin lateral to the eye was the only skin from which overreaction

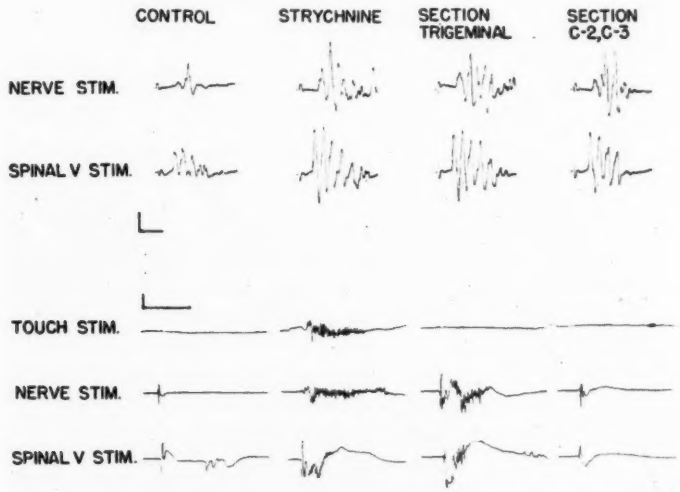


FIG. 10. The upper group of records were recorded from the 2nd division of the trigeminal following stimulation of the infraorbital nerve. The 1st and 3rd divisions of the trigeminal were sectioned before the recording period. Strychnine was then applied over spinal V, 4 mm. below the obex of the 4th ventricle. Marked overreaction followed each single stimulus to the infraorbital nerve, spinal V and touching hair of the face in the cutaneous distribution of the 2nd division of the trigeminal. In this instance there was some pooling of spinal fluid about the strychnine pledget and overreaction to tactile stimuli of the pinna and hair over the upper neck was marked. No overreaction followed stimulation of the skin of other regions. The 2nd trigeminal division was then sectioned distal to the stimulating electrodes. Overreaction persisted unchanged following stimulation of the infraorbital nerve, spinal V and touching fur in the distribution of C2 and C3. Therefore the dorsal roots of C2 and C3 were also severed. No overreaction could then be elicited by tactile stimulation of any region. Nor was there any overreaction following stimulation of the infraorbital nerve or spinal V. The delayed activity, however, in the 2nd division of the trigeminal remained high in amplitude and prolonged in duration following stimulation of the infraorbital nerve or spinal V.

The lower group of records were obtained on a Grass electroencephalogram recorder (time line 1 sec., amp. 50 μV.). Electrodes were inserted into the paraspinal muscles between the scapulae to record the movement associated with the overreaction. Touch stimuli were applied with a fine glass rod to hair in the distribution of the 2nd division of the trigeminal. Nerve stimuli were delivered to the infraorbital nerve. Spinal V stimulation was delivered with small bipolar electrodes just rostral to the cottonoid strychnine pledget. Each vertical group of three tracings corresponds with the nerve recordings immediately above. When there is no overreaction associated with stimulation of the skin in the distribution of C2 and C3 no overreaction persists after complete trigeminal denervation of the skin with stimuli delivered either to the infraorbital nerve or spinal V.

could be elicited by touch after the initial attempt to cut all afferent pathways. With completion of the denervation (usually a portion of the 1st division) overreaction no longer followed electrical stimulation of the infraorbital nerve or spinal V (Fig. 10).

DISCUSSION

As in the chronic animals with overreaction to tactile facial stimulation the interpretation of the behavior of these acute animals must be guarded. The altered state of excitability in spinal V (after strychnine) is in the region of the primary relay nucleus for pain. Larger touch fibers send branches into this region.[7,8] The centrifugally conducted delayed activity recorded in the peripheral trigeminal components is presumably dependent on the integrity of these branches of touch fibers which descend and terminate in spinal V. Hence, although it would seem likely that the quick squint, blink, and struggle following tactile facial stimulation are responses to a painful sensation, severe dysesthesia may be responsible for the altered behavior of these animals.

The constant flow of unsynchronized impulses from cutaneous endorgans may contribute to maintaining a base line of excitability in spinal V. The delayed activity evoked by a single brief stimulus is increased with strychnine applied to spinal V and may be further increased by stroking the face in divisions of the trigeminal nerve adjacent to the one being stimulated (at submaximal intensities). The amplitude, duration and complexity of the delayed activity may reflect an increase in this locally maintained state of central excitability. Furthermore cutaneous denervation (distal to the stimulating and recording electrodes) reduces the delayed activity recorded in the 2nd division with or without strychnine. Presumably the influence of activity from the cell mass of origin of this delayed activity would likewise be reduced in other regions of the central nervous system which it may influence. These three observations are consistent with the above interpretation. This interpretation, however, does not account for the delayed activity not passing the region of trauma in its centrifugal propagation. Nor does it explain why, after incomplete peripheral denervation (distal to the stimulating and recording electrodes) stroking one small area of skin (at times no more than 1 cm. square) will be associated with increased delayed activity and marked overreaction. Finally it is difficult to explain the absence of overreaction in the presence of high amplitude and prolonged delayed activity (evoked either by stimulation of the infraorbital nerve or spinal V) after complete denervation of peripheral skin.

The change in behavior and in the delayed activity after trauma to the posterior root require clarification. There is no clinically demonstrable hypesthesia after the trauma. Evoked cortical responses are not altered. Evoked potentials in spinal V may be clearly reduced in amplitude. Furthermore an electrode in the posterior root proximal to the place of trauma records a delayed activity, somewhat diminished but still of high amplitude,

after the trauma. Centrifugal conduction of delayed activity may be blocked at the site of trauma or by peripheral denervation and under these circumstances stimulation of spinal V results in no overreaction.

Why the delayed activity should not be conducted past the site of trauma while the afferent spike readily enters the brain stem across the same area is not easily understood. It may be that the afferent spike preceding the centrifugal delayed activity by approximately 1–2 msec. at the site of trauma acts as a conditioning stimulus to this portion of the nerve. If the trauma were to prolong the recovery phase sufficiently to keep that region of nerve refractory for 2–3 msec. the delayed activity would not then be able to pass the region of trauma in the course of its centrifugal propagation. That local nerve trauma preferentially blocks conduction of complex potentials more effectively than brief spikes of high voltage is not known.

These findings require that a mechanism be demonstrated in the region of the peripheral sensory endings with which these observations may be consistent. Large fibers that terminate in superficial touch and other end-organs form a dense network in the dermis and subdermal regions. This network surrounds fine pain terminals. These latter structures, being unmyelinated, may be assumed to have the graded response properties of dendrites and other unmyelinated neural elements.[1] By virtue of this characteristic they may be influenced by field potentials. Should these field potentials reach an adequate intensity and persist over a critical duration, pain endings may then initiate conduction of potentials along pain fibers that are in continuity with the active terminals.

If such a thesis is to apply to the present argument, the delayed activity would presumably be great enough when increased by strychnine applied to spinal V to create a critical field potential in the region of the unmyelinated pain terminals in the face, which then secondarily discharge a poorly synchronized afferent volley to the central nervous system. This pain-fiber activation would then be the adequate stimulus for the painful response. This unsynchronized afferent activity has not been recorded. Since no skin reflex has yet been demonstrated this mechanism, suggested in the preceding paragraphs, must remain conjectural.

Properties of the delayed activity in these studies suggest that bifurcating fibers in the trigeminal system may contribute to maintaining the central excitatory state of the cell mass in which they terminate. An afferent impulse conducted over these branches of the trigeminal nerve evokes a complex (and probably in part a transsynaptic) potential at this terminus which is then conducted centrifugally over sensory fibers in the same and adjacent dorsal root elements. It may thereby modify the excitability of sensory end-organs. It may also presumably influence the state of excitability of the central terminus of the primary fiber from which the descending (spinal V) branch stems. There is as yet no evidence to support such a thesis. Although characteristics of the delayed activity in the trigeminal system of cat suggest these possibilities, parallel evidence from other sensory systems must be obtained before these properties of the branches of trigemi-

nal touch fibers that descend to spinal V can be inferred for other circumstances. Bifurcations of large afferent fibers terminating in cell masses other than the terminus of the primary fiber are found in other sensory systems also (visual, auditory, somatic sensory roots). Their function is not understood either in relation to their cell mass of termination or in relation to the parent fiber and its cell mass of termination.

It is tempting to lend significance to these observations by adapting them to explain features of clinical trigeminal neuralgia.[5] None the less we feel that a direct transfer of these findings to humans and clinical settings cannot be fully justified. Twenty-five patients with trigeminal neuralgia and 12 patients with atypical facial pain have been under medical treatment with drugs that have been found to effectively block the delayed activity and the overreaction in cats. When these patients have been followed for 1 year the efficiency of such management will be reported. Even then, however, the demonstration of comparable electrophysiologic phenomena in patients with and without tic douloureux will be essential if these experimental findings are to be considered in some degree valid for adaptation to a clinical counterpart.

SUMMARY

1. Acute preparations in cats have been described in which overreaction to tactile facial stimulation or stimulation of the infraorbital nerve has followed the application of strychnine to spinal V.

2. Simultaneously with the development of overreaction in these preparations there was an increase in the amplitude and duration of centrifugally conducted delayed activity recorded in the peripheral trigeminal divisions.

3. Changes in the overreaction and increased delayed activity following trauma to the region of the semilunar ganglion or posterior root, peripheral trigeminal denervation and the administration of Anectine have been described.

4. The possibility is suggested that this high amplitude and prolonged delayed activity may have to be conducted to the region of peripheral sense organs for overreaction to be apparent.

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OBSERVATIONS IN A CASE OF HYDROCEPHALUS TREATED WITH DIAMOX*

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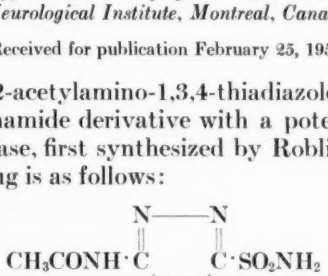
ACETAZOLAMIDE (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide; Diamox) is a sulfonamide derivative with a potent inhibitory effect on carbonic anhydrase, first synthesized by Roblin and Clapp[20] in 1950. The formula of this drug is as follows:



In 1935 Roughton[21] reported the presence of carbonic anhydrase in the red blood cells. This enzyme was shown to act as a catalyst for the reversible reaction $CO_2+H_2O \rightleftharpoons H_2CO_3$. He provided an explanation of the mechanism by which catabolic CO_2 is picked up from the tissues and transported in the blood stream and later released for pulmonary excretion. Since that time carbonic anhydrase has been found to be present in renal cortex, gastric mucosa, pancreas, ciliary body, and brain.[1,2,3,8]

Studies of the pharmacology of Diamox were reported by Maren[15] in 1952, and by Maren *et al.*[17] in 1954. They demonstrated that Diamox lowers the rate of urinary acidification and promotes the excretion of HCO_3^-, Na^+ and K^+ ions which carry excess water with them. The net renal effect of this drug is a diuresis and a mild acidosis. For this reason it has been used in the treatment of cardiac edema, premenstrual tension, and edema of pregnancy.[11] In 1956 Maren[16] reported that in dogs either loss of base or gain of acid in the range of 5–12 mEq./kg. diminished or abolished the typical renal effects of Diamox on excretion of HCO_3.

In addition to its renal effect Diamox exerts an influence on the function of other organs in which carbonic anhydrase is found in high concentrations. It has anticonvulsant properties and has been employed with some success in the treatment of epilepsy. The mechanism of its anticonvulsant effect is, as yet, not completely understood.[6,7,18,19,24]

In 1954 Becker[4] reported the reduction of intraocular pressure in man following oral administration of Diamox. Since that time many papers have

* Presented at the meeting of the Harvey Cushing Society, Detroit, Michigan, April 27, 1957.

appeared in the literature reporting the efficacy of Diamox as a therapeutic agent in the treatment of glaucoma. In 1955 Friedenwald,[10] Kinsey *et al.*[13] and Becker[5] were in agreement on the most likely mechanism by which Diamox decreases the formation of aqueous humor. There is a large amount of carbonic anhydrase in the ciliary body and this enzyme acts as a catalyst for the reaction that results in the formation of H^+ HCO_3^-. The H^+ ion is quickly lost to the blood stream by diffusion and Na^+ enters the eye to form a solution of $NaHCO_3$ which is hypertonic in comparison with its concentration in the plasma. Water then diffuses into the posterior chamber under the influence of osmotic pressure. These conclusions rest heavily upon the findings of Kinsey[12] and others that there is a high concentration of HCO_3^- in the aqueous humor of the rabbit eye. In 1955 Becker[5] reported a reduction of 60 to 65 per cent in rate of flow or production of aqueous humor in rabbit eyes after systemic administration of Diamox. In 1955 Ballintine and Maren[3] found large amounts of Diamox present in iris and ciliary processes of the rabbit after intravenous administration of Diamox (10 to 20 mg./kg.). In 1956 Davson and Luck[9] reported that in man the concentration of HCO_3^- is lower in the aqueous humor than in plasma. Their findings challenge the proposed mechanism of action of Diamox in glaucoma.

In 1954 Tschirgi *et al.*[23] investigated the effect of Diamox on the pressure and rate of flow of spinal fluid in rabbits and cats. They reported that the intravenous administration of 150 mg./kg. of body weight of soluble Diamox was followed by at least a threefold reduction in rate of cerebrospinal fluid flow, or a decline of approximately 30 per cent in intracranial pressure. They believed that the inhibiting effect of Diamox on the rate of formation of H^+ and HCO_3^- within the blood-brain barrier is responsible for a diminished rate of formation of cerebrospinal fluid and interstitial fluid within the brain.

In 1956 Kister[14] studied the effect of Diamox and two allied compounds on the rate of flow of cerebrospinal fluid in cats. He found the rate of flow was diminished 30 per cent after intravenous injection of 0.5 to 150 mg./kg. of Diamox. His studies confirmed those of Tschirgi *et al.* The two other compounds (CL 8490 and CL 13850), closely resembling Diamox chemically but without the inhibitory action of carbonic anhydrase, had no effect on the flow of cerebrospinal fluid. Kister pointed out that no effect of Diamox apart from its action on carbonic anhydrase has been reported. He concluded that the decline in flow of cerebrospinal fluid following Diamox appears to be caused by its inhibitory effect on carbonic anhydrase.

CASE HISTORY

The patient (R.C.) is the eighth in a family of nine children. He was born on April 29, 1951, following a 3-hour labour and normal, noninstrumental delivery. There was a large occipital cephalohematoma but no fracture or unusual separation of the sutures were seen by roentgen ray. The circumference of the head increased from 38.12 cm. on the 9th day of life, to 44.5 cm. on the 27th day. Ventriculography on the 13th day revealed dilated lateral and 3rd ventricles, and failure of

oxygen to pass through the aqueduct of Sylvius. The ventricular fluid was slightly xanthochromic and the protein was 100 mg. per cent.

A diagnosis of noncommunicating, internal hydrocephalus was made and a right ventriculoperitoneal shunt was performed on the 33rd day of life. He was discharged, improved, on the 12th postoperative day (Fig. 1). A revision of the ventriculoperitoneal shunt was necessary on Aug. 11, 1951. The inferior end of the tube had escaped from the peritoneal cavity and symptoms of increased intracranial pressure had developed.

For $3\frac{1}{2}$ years, from August 1951 to April 1955, there was no sign of increased intracranial pressure. He had a left-sided focal cerebral seizure in July 1954, but cerebrospinal fluid pressure was normal.

FIG. 1. Patient at age of 6 weeks (June 11, 1951) after right ventriculoperitoneal shunt.

On May 17, 1955, the patient was readmitted with signs of increased intracranial pressure. These consisted of drowsiness, irritability, vomiting and generalized weakness. There was bulging of the scalp around the tube, and he had papilledema and bilateral Babinski sign. On June 7, 1955, a revision of the ventriculoperitoneal shunt was performed. His condition improved but 2 weeks later a cerebrospinal fluid cyst in the abdomen necessitated an exploratory laparotomy, on June 28, 1955. He was discharged a month later as greatly improved.

Except for one cerebral seizure he did well until Sept. 30, 1955, when, again, symptoms of increased intracranial pressure developed. The circumference of his head was 50.5 cm. and he was noticeably lethargic. There was a nontender mass in the abdomen and subcutaneous fluid was present along the tract of the tube. After 100 cc. of spinal fluid were withdrawn via percutaneous puncture of the tube, the child was much brighter and the cystic abdominal mass disappeared.

Between Oct. 2, 1955 and Nov. 4, 1955, it was necessary to aspirate the tube about once every 4 days. An average of 117 cc. of cerebrospinal fluid were withdrawn each time. Aspirations were performed only after development of signs of increased intracranial pressure, which were lethargy, weakness, anorexia, vomiting, and a tense scalp over the bony defect. With reduction of intracranial pressure there was always dramatic improvement in the patient's clinical picture.

On Nov. 4, 1955, the 4th ventricle was explored and observed to be small. The

aqueduct of Sylvius was not patent and could not be intubated. A right Torkildsen's procedure was performed and the tube was proven to be patent. During a stormy postoperative course, over a period of 52 days, aspiration of the ventriculoperitoneal tube was still necessary, approximately every 2nd day, with an average of 89 cc. of cerebrospinal fluid being withdrawn on each occasion.

On Dec. 27, 1955, a lumbar pneumoencephalogram failed to fill the ventricular system. On the same day 200 cc. of oxygen were injected into the ventriculoperitoneal tube. The lateral ventricles filled, but no gas could be passed into the posterior part of the 3rd ventricle or aqueduct of Sylvius. A radiological diagnosis of a lesion in the posterior part of the 3rd ventricle or aqueduct of Sylvius was made. Subsequently the patient was maintained by a series of ventriculoperitoneal tube aspirations, every 2nd or 3rd day, as before.

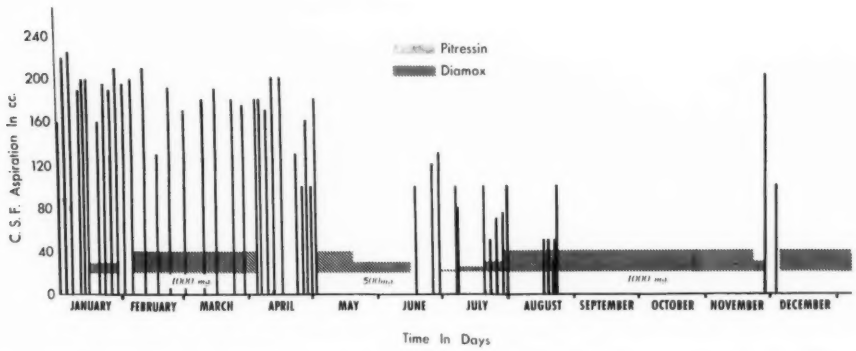


FIG. 2. Summary of 1-year (1956) study of relationship of hydrocephalus (as measured by aspiration of cerebrospinal fluid) to drug therapy. The vertical bars mark the date and amount of fluid removed at each aspiration.

At this point it was felt that the patient provided an unusual opportunity to study the influence of certain drugs on the rate of formation of the cerebrospinal fluid. The required frequency of aspirations (every 2nd or 3rd day) and the average amount of fluid withdrawn at each aspiration were used as base-line data. Trials were made with Pitressin and Diamox. The effect of the Diamox was so striking that we confined the remainder of the study to this drug.

Pitressin failed to have a prolonged effect. On Jan. 15, 1956, 2 units of Pitressin were given by subcutaneous injection every 6 hours. This regimen was continued for 15 days. A transitory effect was obtained and 4 days elapsed without the necessity of aspiration. The base-line conditions were then spontaneously reestablished and aspiration was necessary every 2nd or 3rd day, as before (Fig. 2). Unfortunately efforts to collect 24-hour specimens of urine were unsuccessful. However, he continued to void regularly and catheterization did not seem justifiable.

After a brief drug-free interval a trial of Diamox* was begun Feb. 5, 1956. Diamox, 1000 mg. a day, was given for a period of 2 months. It was administered in 4 oral doses of 250 mg. in order to maintain a continuous high level of activity. Dur-

* This drug was suggested to us by Dr. John Beck of the Royal Victoria Hospital.

ing this period aspirations were noticeably less frequent and became necessary only at 6- to 9-day intervals (Fig. 2). The patient's general condition improved in that he appeared stronger and had a better appetite.

In order to determine whether the favourable change was ascribable to the drug or to some uncontrolled variable, the Diamox was discontinued abruptly. From April 5 to May 2, the patient had no Diamox and the frequency of aspirations increased as before.

On May 2, the Diamox therapy was resumed and continued without interruption for 6 weeks. During this period aspirations never became necessary. A daily dose of 1000 mg. was reduced to 500 mg. at the end of the first 3 weeks. The patient gained strength and improved generally.

The question again arose as to whether the effect was produced by Diamox. The drug was discontinued abruptly for the 2nd time, on June 15. Three days later signs of increased intracranial pressure were evidenced by bulging of the suboccipital craniectomy, drowsiness, irritability, and vomiting. Immediately following aspiration of 100 cc. of cerebrospinal fluid dramatic improvement in the patient's clinical condition occurred. Aspirations were required again on the 11th and 14th days after the drug had been stopped. On each occasion 125 cc. were removed (Fig. 2). The patient's general condition began to deteriorate. It was felt that he had had an adequate trial without the drug, so that Diamox therapy was resumed on June 29, 1956.

As can be seen in Fig. 2, the favourable effects observed during May with 1000 mg. of Diamox continued when the dosage was reduced to 500 mg. daily. Therefore, an attempt was made to establish a minimal daily dose. The daily dose recommended ranges from 5 mg./kg. for a diuretic effect, to a total daily dose of 1000 mg. for the treatment of severe epilepsy or acute glaucoma.

Between June 29 and July 29 a graded series of increasing daily dosages, ranging from 62.5 mg. to 1000 mg., were administered in step-like fashion. Aspirations were required every few days until after the 1000 mg. per day level had been reestablished. This dose represents 80 mg./kg. in our patient and was the maximum daily dose used in this study. From July 29, 1956 to the end of this study in April 1957, the patient remained on 1000 mg. of Diamox daily except for 1 week in November.

FIG. 3. Patient at age of 5 years during present study (July 14, 1956).

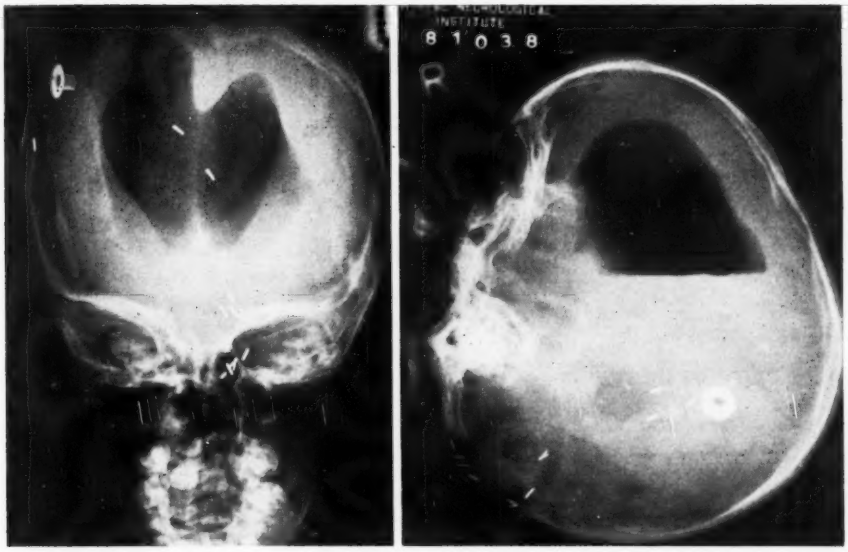


FIG. 4. Pneumoencephalogram via shunt tube during present study (Aug. 23, 1956). Demonstration of degree of hydrocephalus caused by obstruction of aqueduct of Sylvius and posterior part of 3rd ventricle.

Two days after the reestablishment of the maximal dose (July 31) it was necessary to aspirate from the tube. The patient then remained free of increased intracranial pressure for a period of 16 days. During this period of improvement he suffered an attack of measles. Three days after the rash, signs of increased intracranial pressure appeared. Four small (30 and 50 cc.) aspirations were made. On August 23, 100 cc. of spinal fluid and oxygen were exchanged via the ventriculoperitoneal tube. The lateral ventricles were enlarged and the 3rd ventricle was almost completely obliterated (Fig. 4). During this procedure a roentgenogram of the chest, taken in the upright position, revealed no gas in the peritoneal cavity. Following the pneumogram the patient's condition improved and intracranial pressure remained normal. He was discharged home September 15, and continued well. From Aug. 23, 1956 until the end of March 1957 intracranial pressure, as judged clinically, remained normal and aspirations were not required except during 1 week in November 1956, when the dosage of the drug was reduced, as hereafter described.

On November 20, electrolyte studies were made on the blood. A CO_2 combining power of 13.1 mEq./l. was reported; however, Na, K, and Cl were within normal limits. Four days later, November 24, the daily dosage of Diamox was reduced to 500 mg. The following day, November 25, the patient was readmitted because of drowsiness, irritability, and vomiting, although he appeared well hydrated. His vital signs were normal. The suboccipital bony defect was not bulging. However, there seemed to be a small amount of fluid along the subcutaneous tract of the ventriculoperitoneal tube. An emergency CO_2 combining power was reported as 11.6 mEq./l. It was difficult to be certain about the cause of his symptoms. First, we elected to correct the acidosis without further alteration in the Diamox regimen.

FIG. 5. Patient at time of Outpatient Department visit on Oct. 31, 1956.

In spite of vigorous sodium lactate therapy, the patient's symptoms gradually became worse. Three days after admission his CO_2 combining power had risen to 19.2 mEq./l., yet his clinical condition was deteriorating. On that day the skin over the bony defect was tense and it was agreed that the symptoms were most likely caused by elevated intracranial pressure. The tube was aspirated, November 28, and 200 cc. of cerebrospinal fluid were removed. This fluid was under considerable pressure. Oxygen was injected into the tube and radiographs revealed essentially the same picture as seen in the previous encephalogram. The child improved remarkably and almost immediately. He was talkative and active. Diamox was discontinued on that day, November 28, and oral sodium bicarbonate was begun in order to complete the correction of the metabolic acidosis. Six days later aspiration was again necessary and was followed by immediate improvement. Nine days after admission, December 4, the CO_2 combining power was within normal limits, and Diamox, 1000 mg. daily, was restarted the following day, December 5. During the few days that he was not receiving Diamox he had one episode of status epilepticus which began as a left-sided focal cerebral seizure. This had occurred previously in April 1956, during another interval without Diamox.

No further aspirations were required and he remained cheerful and active. He was discharged home on Dec. 22, 1956. Just prior to discharge the CO_2 combining power was reported as 13.4 mEq./l. The daily sodium bicarbonate was increased from 300 to 600 mg. 4 times a day, in a trial to determine its effect on the CO_2 combining power of the blood during Diamox therapy. At the end of 2 months of oral $NaHCO_3$ therapy the CO_2 combining power was 13.5 mEq./l. The administration of the $NaHCO_3$ had not changed, appreciably, the degree of metabolic acidosis induced by Diamox therapy. Since discharge he has been followed in the Outpatient Department, and has remained symptom free, except for the necessity of a single aspiration on April 13, 1957.

DISCUSSION

The patient presented has been shown to be suffering from a noncommunicating type of internal hydrocephalus. The clinical course at the time of this study strongly suggests that the lower end of the ventriculoperitoneal tube was obstructed. In none of the radiological studies was there evidence of communication between the ventricular and subarachnoid spaces. The ventricular spaces required frequent removal of fluid via the shunt tube in order to prevent death from elevated intracranial pressure. These conditions

persisted throughout the 1-year study. The frequency of aspiration and the average amount of cerebrospinal fluid removed was altered markedly during Diamox therapy.

It is our opinion that this drug alters, appreciably, the amount of spinal fluid formed in the ventricles. This view is in keeping with the experimental evidence reported by Tschirgi *et al.*[23] and confirmed by Kister[14] who found a significant decrease in the flow of cerebrospinal fluid in cats after Diamox was given intravenously. This inhibitor of carbonic anhydrase has been shown to decrease the production of aqueous humor in the eye by 60 per cent.[5] Carbonic anhydrase is present in high concentrations in the ciliary bodies and in the substance of the brain. It is worth inquiring, experimentally, whether or not this enzyme plays an important role in the formation of cerebrospinal fluid. Tschirgi *et al.*[23] have suggested that carbonic anhydrase functions at the blood-brain barrier and that it is important in the formation of interstitial fluid as well. If this hypothesis is true, Diamox may be effective not only in altering the production of cerebrospinal fluid but also as a measure in the control of cerebral edema.

The evidence cited in the introduction of this paper supports the hypothesis that the effect of Diamox in epilepsy, glaucoma, and hydrocephalus is a direct one and not secondary to the renal effect. In spite of this preferred mechanism, one cannot rule out the possibility that this patient's response to Diamox is secondary to the drug's renal effect. Indeed the renal excretion of Na^+, K^+, and HCO_3^- must be kept in mind when one considers the electrolytic changes that accompany Diamox therapy.

The electrolyte and urinary studies are summarized in Table 1. After prolonged high daily doses of Diamox (June 14, 1956 and Nov. 20, 1956) the serum Na^+, K^+, and Cl^- are observed to be at border-line low normal levels. The CO_2 combining power is altered considerably and is reported at a level approximately 50 per cent of the lower limit of normal. On both occasions the patient was active, cheerful and asymptomatic. The CO_2 combining power was observed to rise to a normal level quickly following the withdrawal of Diamox (Dec. 4, 1956). It was also observed to fall to the 50 per cent level soon after restarting Diamox in spite of oral administration of 300 mg. sodium bicarbonate daily (Dec. 21, 1956). It is worth noting that the CO_2 combining power on this date (16 days after Diamox was resumed) is almost exactly the same as that found on Nov. 20, 1956, after $4\frac{3}{4}$ months of Diamox daily. Apparently the renal excretory rate of bicarbonate is very high in the period soon after the initiation of Diamox therapy, but levels off at a lower rate which maintains a metabolic acidosis but does not completely deplete the body stores of bicarbonate. The amount of bicarbonate secreted is probably dependent upon the level of acidosis and the amount of bicarbonate present in the plasma. It was observed that after the initiation of the combined therapy of Diamox and sodium bicarbonate the urinary reaction changed from acid to alkaline. This is interpreted as reflecting increased secretion of bicarbonate. It is also observed that the degree of metabolic acidosis was approximately the same as when the

TABLE 1

Laboratory studies of blood, ventricular fluid, and urine during present study

ELECTROLYTE STUDIES

Date	Blood					Cerebrospinal Fluid				
	Na^+	K^+	Cl^-	CO_2	pH	Na^+	K^+	Cl^-	CO_2	Prot.
Jan. 4, 1956										460 mg.%
Feb. 23, 1956						142		420 mg.%		694
Apr. 4, 1956	141.1	3.7	115.0			130	3.3	445		
May 2, 1956	140.5	3.5	101.3			142	3.6	383		
June 14, 1956	140.5	3.7	94.7	16.8						
June 18, 1956	141.0	3.5	116.3	24.6						
June 29, 1956	138.0	5.2	82.8	21.6						
July 5, 1956						142	3.4	399		465
Aug. 23, 1956										700
Nov. 20, 1956	135.0	5.0	107.5	13.1						
Nov. 25, 1956				11.6						
Nov. 26, 1956	135.0	3.1	105.0	16.2	7.37					
Nov. 28, 1956	139.0	3.5	108.6	19.2		141	3.0	395		1660
Dec. 3, 1956										950
Dec. 4, 1956	136.0	4.2	100.0	25.3						
Dec. 20, 1956	145.0	4.4	113.0	13.4						
Feb. 19, 1957	140.0	3.7	114.0	13.5						
Apr. 13, 1957	137.1	4.1	111.0	11.1		138.2	3.37	420.0	13.2	2350

URINE SPECIFIC GRAVITY AND REACTION

Oct. 3, 1956	1.026 Acid	Nov. 27, 1956*	1.006 Alkaline
May 15, 1956	1.022 Acid	Nov. 29, 1956*	1.011 Alkaline
June 16, 1956	1.023 Acid	Dec. 3, 1956*	1.020 Alkaline
July 30, 1956	1.016 Acid	Dec. 11, 1956*	1.018 Alkaline
Nov. 26, 1956	1.022 Acid		

HAEMATOLOGY

Sept. 14, 1956	Complete survey	"Slight leukocytosis"	(11,200)
Dec. 20, 1956	Complete survey	"Neutrophilic leukocytosis"	(12,000)

NORMAL VALUES

Serum electrolytes		*Cerebrospinal fluid electrolytes*
Na 139–148 mEq./l.	CO_2 24–34 mEq./l.	Na Same as serum Na
K 4.3–5.4 mEq./l.	pH 7.37–7.44	K ½ value of serum K
Cl 99–107 mEq./l.		Cl 425–455 mg. %
		Prot. 15–45 mg.%

* Patient receiving Na lactate or Na bicarbonate.

patient was on Diamox alone. These assumptions are compatible with the experimental studies of Maren.[16] He found that in dogs the renal effect of Diamox was greatly diminished by the induction of metabolic acidosis either by loss of base or gain of acid. Thus far this mechanism acts as a safety check for our patient and prevents frank toxicity that probably would be observed if the rate of renal excretion of bicarbonate remained high. In

our patient this degree of acidosis does not appear to be incompatible with a good clinical state.

Toxic manifestations such as paresthesias, drowsiness, cutaneous rash, and agranulocytosis have been reported in isolated cases. None of these has been observed in this patient.

During the above study our patient suffered attacks of chickenpox and measles. The onset of each of these acute febrile illnesses was accompanied by an increase in the frequency of the aspirations of cerebrospinal fluid required in spite of the fact that Diamox therapy was continued. One might wonder if the efficacy of this enzyme inhibitor is decreased in the body during such acute febrile illnesses. Further observations in children might clarify this point.

The patient is known to have infrequent left-sided focal cerebral seizures. He suffered two episodes of status epilepticus during our study and both after sudden withdrawal of Diamox. This is in keeping with the drug's known anticonvulsant property.

In 1953, Sweet and Locksley[22] reported a study of the formation, flow, and reabsorption of cerebrospinal fluid in man. They hypothesized that the protein in the ventricular fluid must move out of the ventricular system and be reabsorbed through the arachnoid villi, whereas the electrolytes diffuse across the brain-fluid membrane in the ventricles and subarachnoid spaces. In our patient the ventricular fluid protein remained elevated throughout. The concentration decreased with the frequency of aspiration, but it was never observed to be less than 400 mg. per cent (Table 1). The electrolytes (Na^+, K^+, and Cl^-) in this fluid remained at relatively normal levels. The elevated protein may be caused by the obstructing lesion or by the presence of the tube. If these possible causes could be ruled out, the persistently elevated protein might be considered as evidence in support of the hypothesis proposed by these authors.

Sweet and Locksley[22] estimated the net production of cerebrospinal fluid which must move out of one lateral ventricle in 24 hours as 15 cc. In our patient the lateral ventricles communicated with each other although the 3rd appeared to be almost completely obliterated. At base-line conditions without Diamox we estimate the 24-hour production in both lateral ventricles to be between 30 and 50 cc.

SUMMARY

1. The effect of Diamox on the formation of cerebrospinal fluid has been studied in a patient with noncommunicating internal hydrocephalus over a period of 1 year.

2. During the administration of Diamox the frequency of aspiration was markedly reduced with long periods when no aspirations were necessary. Percutaneous aspiration of the shunt tube was performed only after signs of increased intracranial pressure developed. Each time the drug was discontinued signs of increased intracranial pressure, again, soon became evident.

3. Proposals concerning the possible mechanism of action of this drug have been made.

4. A brief review of the literature concerning the history and mechanism of this drug is given.

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DISCUSSION

Dr. Leo M. Davidoff: I don't know whether the audience any more than I could be convinced that the medical treatment of hydrocephalus will displace the shunt treatment

presented a few minutes before, but it certainly is interesting to see how these roles parallel each other.

DR. A. EARL WALKER: I wondered in Dr. Branch's presentation how much the acidosis per se had to do with the decreased production of spinal fluid. Supposing these patients were put on a ketogenic diet, would one then see a decrease in the amount of spinal fluid produced?

I also would like to ask as to the amount of urine that was put out during the period when the patient was on Diamox.

DR. JOSÉ L. GARCIA OLLER: I will just mention we have had two years' experience with Diamox. We have had 7 cases. The first one was a brilliant, dramatic result, and most of the others failed.

DR. M. JAVID: This is a very interesting observation. Even though Diamox might have some effect, such as in the case that was described, I think that in situations that neurosurgeons have to deal with urea is much more effective.

The late Doctor Settlage of the Department of Anatomy at the University of Wisconsin and I used this agent for the last 3 years. Effectiveness of urea was compared with other hypertonic solutions and urea was found to be far superior. On this basis I feel the whole question of the use of hypertonic solutions in neurosurgery should be re-evaluated.

As far as Diamox is concerned, in one patient with a "pseudomeningocele," on comparing the effect of urea, Diamox, 50 per cent sucrose, 50 per cent glucose and mercury, I found the result with urea much more impressive. With the aid of our ophthalmological colleagues the intraocular pressure was measured on several patients with acute glaucoma and normal subjects. Comparing urea and Diamox, urea was found to be more effective. The late Doctor Settlage had similar experience with monkeys.

Personal observation with urea extends to about 150 patients. It is a very effective agent in reducing intracranial pressure. We have given it preoperatively, postoperatively, and during surgery. Urea has facilitated operative exposures. It has been life-saving in some of our cases in which postoperative cerebral edema developed. Urea has been quite helpful in some of the patients who were in a critical condition because of increased intracranial pressure preoperatively when temporary control of cerebral edema is most desirable. Also, we have used it, occasionally, during the weekend or at night as a temporary measure until such time that optimum conditions were available for diagnostic studies and surgery.

To sum it up I have found urea so effective that I would hate to be without it.

DR. C. L. BRANCH: Thank you, Dr. Walker for these questions.

Very quickly, we have not tried the ketogenic diet. If you recall the large slide with the many entries, we did produce definitely consistent alkaline urine after large doses of sodium bicarbonate. This was given over a 2-month period from December to February. The amount given daily was 2400 mg., and the child showed no evidence of development of pressure. I don't know whether this is a worth while note or not. But it may possibly be that we probably had a more alkaline condition, that is, we reversed the acidosis and still did not get evidence of increased intracranial pressure.

As far as collecting the amount of urine is concerned, we tried that. However, we had technical difficulties on the pediatric ward and we didn't feel catheterization was justified. So we settled for frequent recordings of the specific gravity.

I am sure you don't recall that slide but there were several entries throughout the study and we had specific gravities of random specimens as high as 1.026 and as low as 1.006. So that we considered that specific gravity stayed within normal limits.

Also in the treatment of cardiac edema, the internists have found that there is a diuresis during the first day of continuous therapy but if the therapy is continued, they are disappointed in the lack of water loss, and so they recommend intermittent treatment with Diamox, and Maren has shown that the effect of Diamox on the renal tubules is greatly diminished in the presence of an acidosis, either by gain of acid or by loss of base in his chronic dogs.

EXPERIMENTAL OCCLUSION OF DURAL SINUSES*

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EXPERIENCE of one of the authors (A.M.M.) in the surgical treatment of wounds of the dural sinuses during the recent Korean conflict, increasing interest in the circulatory anatomy of the brain, and a paucity of specific experimental information led to this study. Efforts were directed toward accumulation of experimental data with regard to questions arising from sudden disruption of the major superficial venous system as encountered in penetrating craniocerebral trauma and also in the presence of space-occupying intracranial lesions.

TECHNICAL DATA

Twenty-eight *Macacus rhesus* monkeys, weighing from 6 to 10 lbs., were used. The dural sinus circulation was exposed by employment of biparietal or bifronto-parietal craniectomy. Intravenous pentobarbital (30 mg./kg.) was used as anaesthetic agent. Surgical alteration of the superficial venous outflow was accomplished by ligation, and by intraluminal insertion of skeletal muscle or paraffin.

Cerebral venous circulation was demonstrated before (Fig. 1), during, and after the experiments by direct sinography with 3–5 cc. of 35 per cent and of 75 per cent Diodrast. Inasmuch as direct sinography did not suffice in every instance to demonstrate collateral circulation, additional bilateral carotid arteriography was carried out in 5 animals.†

Unipolar and bipolar electroencephalographic recordings were made in the parietal regions of 5 animals before, during, and after sinus occlusion, using an Offner 4-channel electroencephalograph. Simultaneous cerebrospinal fluid pressure readings were obtained through a #18 spinal needle inserted in the cisterna magna and connected to a water manometer.

Gross and microscopic examinations of specimens of brain and dural sinus were obtained from 16 animals, sacrificed from 5 days to 6 months after completion of the experiment. All types of occlusion were represented.

Microscopic studies of dural sinuses containing intraluminal skeletal muscle were made.

EXPERIMENTAL DATA

I. *Occlusion of Rolandic and Bridging Veins* (8 monkeys). Bilateral occlusion of the Rolandic veins was produced in 3 animals. This resulted im-

* This study was supported by the Research and Development Division, Office of The Surgeon General, Department of the Army, under Contract No. DA-49-007-MD-522.

† Sinograms and arteriograms were made by Mr. James Hamlin, Chief X-ray technician, Vanderbilt University Hospital.

FIG. 1. *Monkey 345.* Sinogram without alteration of venous system.

mediately in intense but transitory bilateral cortical swelling. Simultaneously marked distention of the superficial venous channels took place. A neurological deficit did not develop.

In 3 animals all venous tributaries of the superior longitudinal sinus were interrupted bilaterally. Again transitory, intense, bilateral cortical swelling and distention of the superficial cortical veins took place. The animals survived without development of a demonstrable neurological deficit.

In 2 animals unilateral interruption of the venous tributaries to the superior longitudinal sinus was produced. This resulted in homolateral edema and in homolateral distention of cortical veins. These animals also survived without development of a demonstrable neurological deficit.

Attempts at demonstrating the collateral network by means of sinography failed in all 8 animals. For that reason bilateral carotid arteriography was performed in 5 of the 8 monkeys in an effort to visualize in the venous phase the collateral network produced by occlusion of all venous tributaries to the superior longitudinal sinus. This was successful in 1 animal only (Fig. 2). The animal, however, expired immediately following the injection of the dye, which might account for the radiographic success. Postmortem examination of the brain of all 8 animals failed to reveal any significant gross or histological pathology.

II. *Occlusion of Superior Longitudinal Sinus Anterior to Rolandic Veins* (3 monkeys). Occlusion of the superior longitudinal sinus anterior to the Rolandic veins was produced in 3 animals by ligation with 0000 silk. Occlusion of the sinus at site of ligation was demonstrated in each instance by sinography.

Ligation did not produce an alteration in the cerebrospinal fluid pressure.

Electroencephalographic studies immediately after ligation revealed a variable momentary burst of slowing with elevations of slight amplitude. Postmortem examinations did not reveal any gross or microscopic pathological changes.

III. *Occlusion of Superior Longitudinal Sinus Posterior to Rolandic Veins* (16 monkeys). Occlusion of the superior longitudinal sinus posterior to the Rolandic veins was produced in 16 monkeys. This was accomplished by

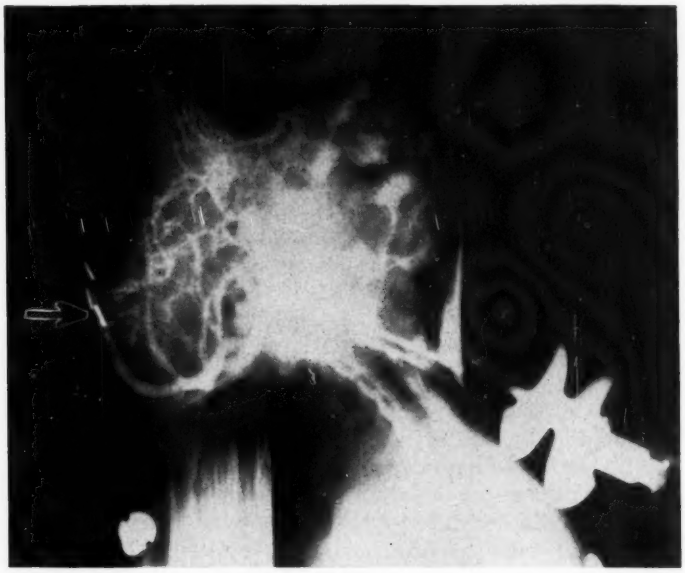

FIG. 2. *Monkey 348.* Bilateral carotid arteriogram with venous phase demonstrating collateral drainage following bilateral clipping of Rolandic vein.

ligation in 8 animals, by injection of hot paraffin into the sinus in 3 animals, and by insertion of skeletal muscle into the lumen of the sinus in 5 animals. That portion of the sinus that had been occluded by insertion of skeletal muscle was excised in all 5 monkeys after a period of 15 days and the sinus was ligated proximally and distally. In each instance, occlusion of the posterior third of the superior longitudinal sinus was confirmed by sinography. The uniform response to occlusion consisted of cerebral edema and profound bilateral engorgement of cortical veins. A demonstrable neurological deficit did not occur.

In 5 animals electroencephalographic studies and determination of changes in the cerebrospinal fluid were carried out in order to obtain further information on the effect of sudden alteration in venous outflow. In each instance slow waves of high amplitude (200 to 300 μV., 3 to 5 per sec.)

occurred instantaneously and returned gradually, within 20 to 90 sec., to the baseline pattern (Fig. 3). Associated with the appearance of the slow waves of high amplitude was a rise in cerebrospinal fluid pressure, with increases ranging from 70 to 100 mm. H_2O. A plateau of 70 to 100 mm. H_2O above the pre-occlusion pressure was reached in each case within 1 to 2 min. These levels remained unchanged at termination of the experiments 4 hours later.

Injection of hot paraffin into the lumen of the sinus produced immediate occlusion in 3 animals. At periods of 2, 4 and 8 weeks respectively, the paraf-

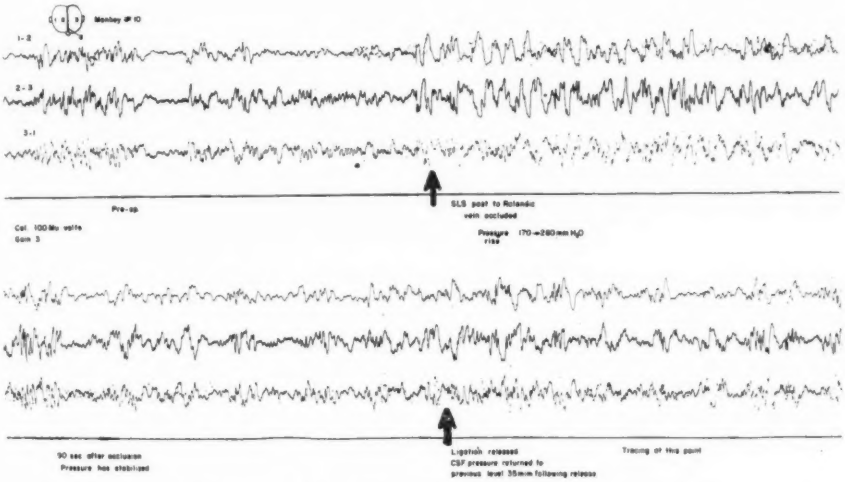
Monkey # 10
1-2
2-3
3-1
Pre-op
SLS post to Rolandic vein occluded
Pressure rise 170 → 280 mm H₂O
90 sec. after occlusion Pressure has stabilized
Ligature released CSF pressure returned to previous level 35 mm following release
Tracing of this point

FIG. 3. *Monkey 10.* Electroencephalographic and cerebrospinal fluid changes before, during and after occlusion of the superior longitudinal sinus posterior to Rolandic inflow.

fin was removed. Formation of a thrombus was not induced by this method of occlusion. Removal of the obstructing paraffin resulted in restoration of normal venous outflow demonstrated by sinography.

Insertion of skeletal muscle into the lumen of the sinus resulted in complete obstruction which was demonstrated by sinography 1 week following occlusion. Relief of the obstruction and recanalization had taken place in all 5 animals when sinography was repeated 2 weeks after occlusion (Fig. 4). During these 2 weeks no demonstrable neurological deficit developed. The sinus was then resected at the site of muscle insertion for purpose of histological studies. It was of interest to note that ligation of the sinus proximally and distally did not produce a neurological deficit.

Histological studies revealed conversion of the muscle into collagenous scar tissue which was firmly adherent to the wall of the sinus except at the site of recanalization (Fig. 5). These sites were characterized by islands of

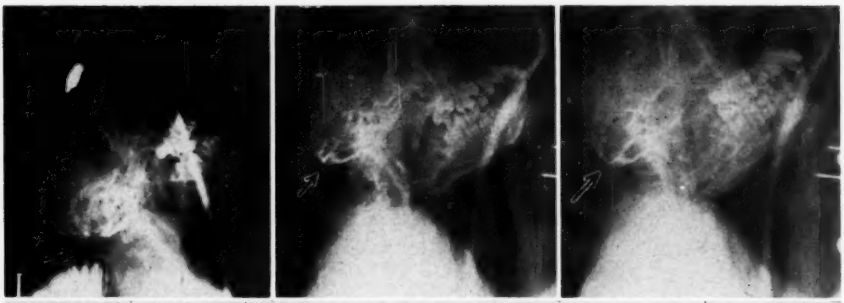

FIG. 4. *Monkey 7.* (A) Sinogram immediately following insertion of muscle occluding the superior longitudinal sinus posterior to Rolandic veins. (B) Sinogram 9 days following occlusion. Note appearance of Diodrast distal to site of occlusion. (C) Sinogram following excision of superior longitudinal sinus containing muscle.

partly degenerated muscle fibers surrounded by spaces which were lined with endothelial cells and which contained blood elements (Fig. 6). Large spaces between scar tissue and wall of the sinus appeared to be continuous with the sinus. There was no evidence of thrombus formation.

Sinography was carried out at varying intervals following permanent occlusion of the sinus in 9 monkeys, demonstrating the development of collateral routes about the site of obstruction (Fig. 7).

A neurological deficit was not observed in any instance. Gross and micro-

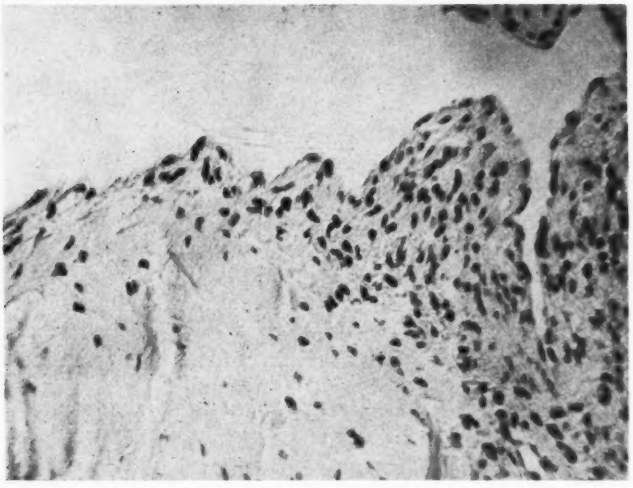

FIG 5. *Monkey 7.* Section through superior longitudinal sinus demonstrating endothelial lining of muscle. (220×)

FIG. 6. *Monkey 130.* Section of superior longitudinal sinus showing muscle infiltrated with red blood cells and enlarging channels. Sinus excised 2 weeks following occlusion with muscle. (220×)

scopic examinations did not reveal any pathological changes other than those described in the presence of skeletal muscle.

IV. *Occlusion of Lateral Sinuses* (1 monkey). Ligation of both lateral

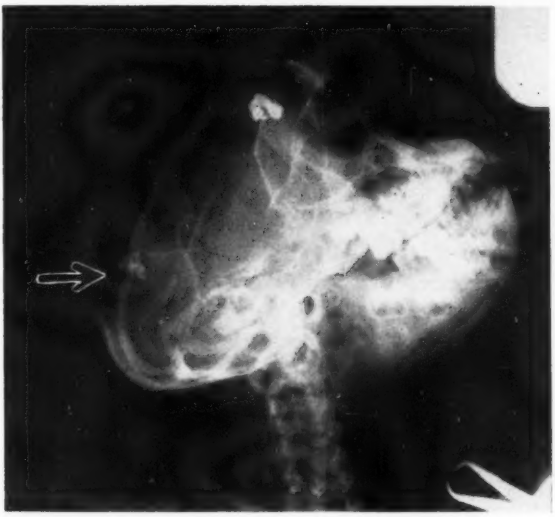

FIG. 7. *Monkey 394.* Sinogram 3 months following occlusion by ligation of superior longitudinal sinus posterior to Rolandic vein. Large numbers of collateral channels are present at site of occlusion.

sinuses was performed just proximal to the torcular Herophili. Electroencephalographic wave patterns and changes in cerebrospinal fluid pressure followed closely those seen in the presence of occlusion of the superior longitudinal sinuses. Time factors were similar, with the electroencephalogram returning to the pre-occlusion pattern within 70 sec. The cerebrospinal fluid pressure, when recorded after 4 hours, at time of termination of the experiment, remained elevated as had been observed in the presence of occlusion of the superior longitudinal sinus. Subsequent pressure readings, though desirable, were not obtained because it was felt that conditions would not be comparable.

V. *Comments on Experimentally Attempted Induction of Sinus Thrombosis.*

1. Intraluminal injection of hot paraffin, though productive of immediate permanent occlusion of the sinus, did not lead to formation of a thrombus.

2. Intraluminal insertion of skeletal muscle, though productive of transitory occlusion of the sinus, did not lead to formation of a thrombus.

3. Efforts to produce a thrombus by direct trauma applied to various portions of the superior longitudinal sinus in the presence of artificially induced hypotension failed to result in formation of a thrombus.

DISCUSSION AND CONCLUSION

In man the analysis of neurological sequelae to occlusion of dural sinuses or their tributaries has been complicated by associated gross cerebral lesions and simultaneous pathological alterations of collateral routes. Nevertheless Holmes and Sargent[3] have been able to define a neurological syndrome occurring in man with occlusion of the superior longitudinal sinus posterior to the Rolandic veins. Merwarth[5] described the Syndrome of the Rolandic Vein. The recent observations of Swanson and Fincher[7] throw additional light upon the nature of the neurological deficit resulting from obstruction of the sinus. All authors agree that the superior longitudinal sinus can be ligated with impunity anterior to the point of entrance of the Rolandic veins. This has been confirmed by an analysis of 112 wounds of the dural sinuses incurred in the Korean War.[4] There is considerable evidence, in the latter analysis and in Swanson and Fincher's observations, that the dire neurological sequelae to occlusion of the dural sinus posterior to the Rolandic veins may be temporary, and that extent and duration of the neurological deficit may depend on the local damage that has been produced.

Beck and Russell[1] have attempted to produce thrombosis in the superior longitudinal sinus of dogs and cats by introduction of agents usually productive of thrombotic lesions elsewhere. A neurological deficit did not result in those animals. Swanson[6] was unable to produce thrombosis of the superior longitudinal sinus of the monkey by ligation. Even after resection of the posterior longitudinal sinus of 1 monkey, a neurological deficit did not develop during a 9-month follow-up period.

The present study confirms Beck and Russell's observation in dogs and cats and those of Swanson in the monkey. Thrombus formation did not

occur in any of the animals. A neurological deficit did not result from occlusion of the Rolandic veins or of the superior longitudinal sinus posterior to the Rolandic veins.

The experimental evidence of cortical swelling and venous engorgement, associated with an increase in the cerebrospinal fluid pressure and with changes in the electroencephalographic pattern, indicate temporary alterations similar to those expected in man. The apparent rapid development of collateral venous outflow, as demonstrated in the monkey, seems to prevent permanent alterations. These experimental studies lend added weight to Swanson and Fincher's observations[7] and to the analysis of war wounds involving dural sinuses to which we have referred at the outset of this discussion.[4]

As in the monkey, the electroencephalogram may be helpful in man in assaying the immediate effect of occlusion. Transient occlusion followed by gradual improvement of the electroencephalographic record may well provide a measure of the ability of the collateral circulation to return the pooling venous blood to the heart.

By the establishment of adequate venous drainage, Cairns *et al.*[2] have shown that a large muscle stamp does not necessarily interrupt the flow of blood through a sinus so repaired. The analysis of wounds of the dural sinuses incurred in the Korean War[4] revealed 1 instance of secondary thrombosis in 15 lacerations of the sinus that were repaired with a muscle stamp. That analysis furthermore suggested that the occurrence of secondary thrombosis depends not so much on the method of repair as on the maintenance of blood volume and pressure before, during, and immediately after operation. Beck and Russell[1] have pointed out the effectiveness of reparative processes ending in organization and recanalization of the occluding muscle or of the cotton wool in the dog. The response of intraluminal striated muscle in the present series of experiments confirms the concept of recanalization. The value of the use of muscle stamps as method of choice for the repair of extensive lacerations of the sinus has been suggested previously on the basis of clinical observations. The current study demonstrates the process of recanalization which takes place in a sinus that has been repaired with a muscle stamp.

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HYPOTHERMIA ANESTHESIA IN THE SITTING POSITION

REPORT OF TWO CASES OF ACOUSTIC NEURINOMA*

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IN AN editorial appearing in the March 1950 issue of *Surgery, Gynecology and Obstetrics*, Horrax[3] remarked that "the removal of an acoustic tumor is, by and large, the most serious and potentially hazardous operation of all those undertaken for intracranial new growths." He went on to say that "the five year mortality for the intracapsular procedure is between 50 and 60 per cent, and the chance of useful survival is not over 40 per cent, probably less. For complete removal the five year mortality varies from 12 to 25 per cent, and the useful survival figure is at least 65 per cent. From these data, it would appear that primary, complete extirpation of acoustic tumors is the surgical procedure of choice."

In 1949, Atkinson[1] clearly demonstrated that the postmortem finding of malacia pontis following removal of acoustic neurinoma is caused by occlusion of the anterior inferior cerebellar artery or one of its branches. Thus, the problem of total removal of acoustic neurinoma is twofold: first, the actual size of the lesion and second, preservation of the blood supply to the brain stem. Atkinson pointed out that there is a decrease in the number of functioning anastomotic branches between the anterior inferior and posterior inferior cerebellar arteries following cerebellar resection and compression of this structure, which is a necessary step for removal of a large acoustic neurinoma. In addition, he noted that there may be associated spasm of the arterial branches of the anterior inferior cerebellar artery when the main branch is occluded; this also holds true for their collateral anastomoses with adjacent arteries. Therefore, these vascular changes may contribute to infarction of the brain stem. Atkinson reached the conclusion that there is grave danger to the patient if the anterior inferior cerebellar artery is occluded during operation on an acoustic tumor because of the possible damage to the autonomic pathways in the lateral portions of the tegmentum of the brain stem.

On the other hand, in 1955 McKenzie,[5] in discussing operative treatment, observed that in order to carry out a total removal of acoustic neurinomas the anterior inferior cerebellar artery is invariably clipped and di-

* Presented at the semiannual meeting of the Southern California Neurological Society, December 1956.

vided. He concluded that: "In all probability surgeons will have an irreducible mortality in the neighborhood of 10 per cent because of the importance of this artery."

Recent studies, such as those carried out by Rosomoff[6] in 1956, have demonstrated that following experimental surgical interruption of the major cerebral arteries during hypothermia anesthesia no infarction developed, or if small lesions were found they were restricted to relatively silent areas. The temperatures were reduced in experiments on dogs to 22–24°C. In this study Rosomoff pointed out that there is a reduction of blood flow that facilitates hemostasis and a decrease in the brain volume that enhances surgical exposure and diminishes intracranial pressure.

With few exceptions, acoustic neurinomas are now being approached surgically with the patient in a sitting position. This poses the problem of postural hypotension and air embolism. Gardner[2] has recently dealt with hypotension by using an inflatable cuff over the lower extremities. McKenzie[5] stated that the risks of air embolism and hypotension are outweighed by the advantage of properly visualizing the line of cleavage between the tumor and the brain stem in a relatively bloodless field.

TECHNIQUE OF HYPOTHERMIA IN THE SITTING POSITION

Hypothermia anesthesia was performed in the sitting position on 2 young female patients with huge acoustic neurinomas in an effort to avoid the possible complication of malacia pontis after clipping and dividing the anterior inferior cerebellar arteries during the total removal of the tumors. Anesthesia was induced with intravenous Surital and tracheal intubation with the aid of succinylcholine for relaxation. Anesthesia was maintained with nitrous oxide and small fractional doses of Surital. Chlorpromazine was not employed because of its hypotensive effect as a result of autonomic blockage. Three standard electrocardiographic limb leads were applied to monitor the electrocardiographic actions on an oscilloscope. The patients' lower extremities were wrapped in elastic bandages or encased in elastic stockings from the toes to the groins. The patients were then placed in the supine position between the large precooled Therm-O-Rite blankets. They were then raised gradually to a sitting position, using the American Sterilizer table and the Craig headrest (Fig. 1). In each instance, the temperature was lowered to 30°C. The electroencephalographic leads placed over the frontal, parietal, and temporal regions made continuous recordings. While hypothermia was being induced, the right brachial artery was cannulated under direct vision to permit constant intra-arterial pressure readings. The radial arteries were not used because of insufficiency of the ulnar artery. A venous cutdown in the same arm was employed for intravenous infusions. One bottle of intravenous solution containing a vasopressor agent was on hand to offset a possible fall of the systolic blood pressure below 100 mm. of mercury. The patients were draped in such a fashion as to allow for immediate thoracotomy and cardiac massage in the event of cardiac arrest.

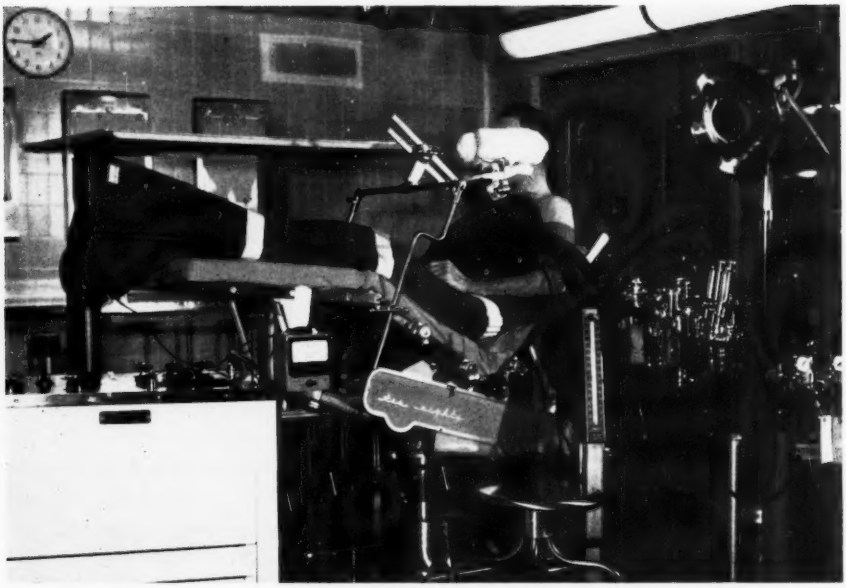

FIG. 1. Photograph of sitting position used during hypothermia anesthesia. Therm-O-Rite blankets, pump and thermometer are in place.

Instruments for thoracotomy and cardiac stimulants were available in the operating room.

The temperature of 30°C. was reached in each instance prior to occlusion and division of the anterior inferior cerebellar artery. In the first patient a delay in reaching 30°C. occurred because only one blanket was used. The sitting position of the patient resulted in kinking the tubes within the single blanket and stopping the circulation of the coolant. When a second blanket was added the temperature promptly dropped to the desired level. This complication did not occur in the second patient when two blankets were used (Fig. 1). The temperature of 30 C. was maintained until removal of the tumor was accomplished and closure was commenced. At no time was there any sign of cardiac disturbance in either patient, and at no time did the systolic blood pressure drop below 90 mm. of mercury. As a matter of fact, the anesthetic chart of Case 1 showed a marked hypertension until the 30°C. level was reached, at which time pressures fell only to mild hypertensive levels. The blood pressure in Case 2 was essentially in the low, normotensive range with one episode of severe hypertension. At no time were alarming hypotensive levels approached.

The patients were allowed to warm and regain full control of their medullary centers. Tracheotomy was performed immediately after the operation in both instances to facilitate postoperative care. In Case 2 an

immediate tarsorrhaphy was performed; in Case 1 this procedure was done on the 4th postoperative day to treat an early neuroparalytic keratitis.

The patients made remarkably uneventful recoveries without any significant disturbance of fluid or electrolyte balance. Each patient maintained a low-grade elevation of temperature for a week or 10 days after operation, apparently because of the blood in the subarachnoid space and contusion of the resected cerebellar lobe. Postoperatively, no neurologic sign suggestive of infarction of the brain stem occurred. In fact, improvement of preoperative neurological deficits was noticeable in 7 to 14 days.

CASE REPORTS

Case 1. M.F., a 42-year-old widowed, former professional pianist and organist, in 1951 noted the onset of a roaring sound of the left ear and loss of certain high tones within a musical chord. Two years later the hearing had decreased markedly in the left ear. Concomitantly, incoordination developed in her gait, as well as in the left upper extremity and she also noted a numbness on the left side of the face that involved the upper lip, cheek, forehead, and side of the tongue. By 1955, it was evident that her speech was slurred and that she had difficulty in swallowing, with a tendency to regurgitate fluids through her nose.

Examination on admission in September 1956 revealed early bilateral papilledema. Marked nystagmus on right and left lateral gaze and a rotary type of nystagmus on upward gaze were present. The corneal reflex on the left was completely absent. Hypesthesia and hypalgesia existed on the left side of the face, together with suggestive weakness of the left temporalis and masseter muscles. A partial peripheral type of left facial weakness was observed. The left labyrinth was completely unresponsive with almost total deafness on that side. The pharyngeal reflex was absent on the left and the patient's speech was markedly slurred. The tongue tended to deviate to the left. Marked ataxia in the left upper and lower extremities with other signs of dyssynergia were found; motor strength was unimpaired. She walked on a broad base and staggered to the left. The deep tendon reflexes on the left side were hypoactive as compared to the right.

Roentgenograms of the skull revealed a wide funnel-shaped porus acusticus on the left consistent with acoustic neurinoma.

Routine laboratory studies were within normal limits. The opening cerebrospinal fluid pressure was 230 mm. of water; the closing pressure was 180 mm. The fluid was xanthochromic and contained 263.5 mg. of protein.

Diagnosis. Left acoustic neurinoma.

Operation. On Oct. 22, 1956, a huge, partly degenerated, acoustic neurinoma which extended from the foramen magnum through the incisura, markedly compressing the brain stem, was uncovered by Dr. Paul H. Crandall. After the lateral half of the cerebellar hemisphere was resected, the tumor was totally removed according to the technique described by McKenzie.[5] No noticeable damage to the brain stem occurred during this dissection. The wound was closed in the usual fashion. The patient tolerated the hypothermia anesthesia in the sitting position quite well, but maintained a moderate to marked degree of hypertension throughout the procedure.

Course. The patient had an immediate low-grade febrile course which gradually subsided. At no time did she show significant electrolyte or fluid imbalance. She

was fed for the first week by nasal gastric tube following the discontinuation of intravenous feedings 48 hours after surgery. Tracheotomy performed immediately after surgery provided a satisfactory airway and seemed to play a major role in the postoperative course. Tarsorrhaphy was done 4 days after surgery because of an early neuroparalytic keratitis. On Nov. 8, 1956, a left hypoglossal-facial anastomosis was carried out under general anesthesia. The patient had an uneventful recovery and was discharged.

Case 2. L.A.S., a 25-year-old housewife, awoke one morning in mid-March 1956, with numbness and tingling of the left side of her body and head, weakness of the left extremities, and deafness and tinnitus in the left ear. These symptoms progressed slowly in intensity and soon became associated with left facial weakness, unsteadiness of gait, slurring of speech, and decreased visual acuity. On direct questioning she described the frequent occurrence of severe suboccipital headaches and occasional dizzy spells with facial flushing over the past 4 years.

Examination. On admission on Oct. 2, 1956, early papilledema was found. The visual acuity O.U. was 20/20 with normal peripheral and central fields except for enlarged blind spots. Nystagmus of a marked degree was found on left and right lateral gaze with a rotatory type on upward gaze. The sensory portion of the left trigeminal nerve was completely involved but only a partial motor loss was found. Moderate weakness of the entire left side of the face with associated loss of taste on that side was present. Loss of hearing in the left ear of nonconduction type was severe to the point of clinical deafness. Moderate loss of conduction was also present on the right. The gag reflex was absent bilaterally and the uvula rose to the right side. The vestibular test on the right was normal; on the left there was no response. The spinal accessory and hypoglossal nerves were intact.

Marked ataxia of the left extremities was present with staggering of gait and a tendency to fall to the right. In addition, an almost athetoid movement of the left upper extremity existed during finger-to-nose testing.

No definite involvement of pyramidal tract or medial lemniscus was found. The superficial and deep tendon reflexes were essentially normal with plantar responses being flexor.

At lumbar puncture the opening pressure was 230 mm. of water. The fluid was very slightly xanthochromic containing a total protein of 314 mg. per cent and a colloidal gold curve of 555432110. The Pandy was 3+. The electroencephalogram and the electrocardiogram were normal. Roentgenograms of the skull showed erosion and funnelling of the left porus acusticus. Planograms of the petrous bones confirmed these findings. Roentgenogram of the chest was normal.

Diagnosis. Left acoustic neurinoma.

Operation. Total removal of a very large acoustic neurinoma which extended from the incisura to the foramen magnum was performed.

Course. The patient responded immediately after anesthesia and had an uneventful convalescence. As in the first case, nasal gastric-tube feeding was used until she could swallow easily. A left hypoglossal-facial nerve anastomosis was performed on Nov. 15, 1956. Recovery was uneventful.

DISCUSSION

Although the risk of hypothermia is added to hazards generally present when an effort is made to do a total removal of an acoustic neurinoma, it is

felt that these 2 cases serve to illustrate that such a procedure is feasible and may be carried out with relative safety. And, in the future, lower hypothermic levels may be utilized to give added protection to the brain stem. Careful attention must be given to the preoperative cardiovascular status, position of the patient, and blood pressure during operation. The intra-arterial pressure readings were about 20 mm. of mercury above those taken with the usual balloon sphygmomanometer.

It is apparent, of course, that in approximately 90 per cent of patients, according to McKenzie,[5] total removal of an acoustic neurinoma may be accomplished without producing significant malacia pontis. Thus, these 2 patients may well have fallen into this major group. It is felt, however, that hypothermia significantly helped them survive during their operative procedure as well as during the postoperative period. It is believed that, in selected cases, hypothermia anesthesia in a sitting position will reduce the mortality of total removal of acoustic neurinomas below 10 per cent by avoiding infarction of the brain stem. This technique may also be of value in the neurosurgical approach to vascular tumors and anomalies in the posterior fossa. Recently, since these initial experiences, a third patient with a vascular lesion of the anterior portion of the circle of Willis was operated upon successfully by Dr. Theodore Kurze.[4] The sitting position with a modified position of the head and hypothermia anesthesia of 29–30°C. were employed. The visualization of the pathology was excellent. The patient tolerated this position and the hypothermia without significant hypotension or other changes in vital signs. Various anti-G suits for lower extremities and abdomen are now under study in an effort to determine their adaptability to hypothermia anesthesia in the sitting position for neurosurgical problems.

SUMMARY

A new technique employing hypothermia anesthesia in a sitting position has been presented. Its value for various types of neurosurgical procedures has been discussed.

ADDENDUM

Since submission of this paper for publication 3 additional patients have been operated upon by the various members of the staff, employing hypothermia anesthesia in the sitting position. The first patient, a 22-year-old female, was explored for a probable cerebellopontine-angle tumor. The temperature was lowered to 30°C. The second, a 52-year-old male, harbored an aneurysm of the anterior communicating artery. The temperature was decreased to 28°C. The aneurysm was successfully isolated between silver clips. The most recent problem was an arteriovenous malformation of the right occipital lobe in a 15-year-old boy. The temperature was lowered to 30°C. during the successful resection of the lesion. Normotensive blood pressure levels were maintained in all of these patients without the use of vasopressor drugs. The patients tolerated hypothermia anesthesia in the sitting position without complications.

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EXPERIMENTAL CINGULUMOTOMY AND MODIFICATION OF MORPHINE WITHDRAWAL*

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WITHDRAWAL of morphine from the addicted individual has been a clinical problem for many years. The neurological problems in addiction and withdrawal are poorly understood and laboratory investigations have been few.[16,29,30,36,41] The manner in which the nervous system becomes dependent upon this drug and the precise fashion in which the function of the nervous system is deranged in the withdrawal syndrome remain unknown. Several clinical techniques have been used to reduce or obscure the effects of withdrawal, such as severe insulin-induced hypoglycemia,[3] metrazol-induced convulsions,[3] electroshock therapy,[15,31] steroid therapy, and prefrontal lobotomy. Only prefrontal lobotomy, however, gives any degree of differential modification of symptoms of withdrawal that might aid in understanding the neurophysiological derangements present when the drug is withdrawn.

Modification of the syndrome of morphine withdrawal by prefrontal lobotomy has been recognized clinically since 1946.[26] Even so, there has been prolonged disagreement as to whether this procedure relieves the signs and symptoms completely[12,17,26–28] or simply modifies them.[6,14,22,34,40] There is as yet no generally accepted basis for these effects, and explanations have varied from loss of psychic craving[21] to simple obscuration of the abstinence syndrome by postoperative lethargy and loss of integrated cerebral activity as a result of extensive damage to the brain or "diaschisis."[40]

The lesions included in frontal lobotomy vary a great deal since varied technical procedures are used to sever the frontal fiber tracts. The resulting variability of the lesions could be the cause for the divergent opinions on the effects of frontal lobe lesions on the abstinence syndrome. A few careful pathological studies have shown this variability and likewise indicate that only two fiber tracts, the cingulate fasciculus and the uncinate fasciculus, are consistently sectioned in the usual frontal or prefrontal lobotomies.[22,23]

Previous experiments have shown the reliability of producing morphine

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Part of these data is included in medical thesis presented to Faculty of University of Washington School of Medicine, Seattle, May, 1953 (L.E.W.).

† Markle Scholar in Medical Science.

addiction and studying effects of withdrawal of the narcotic in both dogs[36,37] and monkeys.[16,29,30] Thus, experimental abstinence produces signs and symptoms generally related to one of two groups—(1) The "psychic" or "purposive dependence" group, and (2) the "somatic" or "nonpurposive dependence" group.[36] The former group of signs and symptoms has been related to psychic drives in which a strong volitional element on the part of the addict exists, and the latter group has been presumed secondary to effects on the autonomic system with no volitional element involved. This more or less arbitrary division might be used to study the selective effects of specific lesions of the frontal lobe on the syndrome of experimental abstinence.

The original purpose of this study was to determine what effects certain selective lesions of the frontal lobe might have on the "psychic" and "somatic" components of experimental withdrawal of morphine in monkeys In view of observations already made, the frontal lobe lesions selected for study were frontal lobectomy,[10,25,36] resection of the cingulate gyrus,[18,19,32,33] and stereotaxic cingulumotomy.[7] Thus, the lesions ranged from massive loss of the frontal lobe to minimal physical lesion in the cingulum. Bilateral and unilateral lesions were studied because of previous controversies.[27,38,40] Control procedures were designed to rule out the effects of the operative exposure and massive removal of brain in regions other than frontal lobe.

A secondary purpose was to determine briefly if a similar chronic frontal lobe lesion could change the susceptibility to addiction or cause a persistent alteration of the abstinence syndrome.

METHODS

Fourteen monkeys (*Macaca mulatta*), 6 males and 8 females, were used in the chronic series of experiments. All animals were immature, and weighed from 3 to 5 kg. Ten animals were addicted to morphine sulfate, and 12 operative procedures were carried out on 8 of these animals (Table 1). Of the remaining 2 addicts, 1 died in acute morphinism, and 1 died in morphine withdrawal. One animal was used for an anatomical control, 2 were used for pharmacological controls involving Nalline,* and 1 was given saline injections for a control on the production of addiction. Table 1 shows the basic outline of this series of experiments and diagrams the sequence in which each animal was used in the serially arranged schedule of procedures.

Addictions. All animals were addicted to morphine sulfate by the method originally described by Kolb and DuMez.[16] For 4 to 6 weeks, injections of morphine sulfate were given subcutaneously twice daily in increasing doses until the animal tolerated a daily dose of 135 to 200 mg. Evidences of addiction[16,29] appeared as a rule on the 8th to 9th day of injections. An animal receiving morphine injections was considered to be addicted when cessation of morphine injections resulted in an unequivocal withdrawal syndrome.

All animals to be addicted were observed carefully for a period of 2 weeks

* Kindly supplied by Merck & Co.

prior to addiction in order to establish and record patterns of their individual and group activity. During the addicting period they were observed twice daily, before and after the morphine injections. Their activity was compared with that of the monkey receiving saline injections as well as their own previous pre-addiction activity. In all cases, two periods of controlled withdrawal were carried out prior to any operative procedure. This established the individual withdrawal syndrome for each animal. After withdrawal, addiction was rapidly re-established at the same dosage and subsequent withdrawals were carried out at intervals of 2 weeks or longer.

Preoperative Withdrawal. Morphine withdrawal was accomplished by either standard withdrawal or by Nalline-induced withdrawal. In the standard withdrawal group, the injections were stopped after an afternoon injection and the animal was carefully observed during the subsequent 3 days for apprehension, salivation, yawning, rhinorrhea, lacrimation, anorexia, pilomotor activity, muscle twitches, abdominal cramps, restlessness, irritability, conjunctival inflammation, and diarrhea. These signs have been established previously as characteristic of morphine withdrawal in the monkey.[16,29,30]

Nalline-induced withdrawal was accomplished by subcutaneous injection of 5 or 10 mg. of Nalline (n-allylnormorphine hydrochloride) as described by Wikler.[35,37–39] Since a full withdrawal syndrome occurred within 2 to 5 min. with this technique, careful observations of the animals' activities were necessary for only 2 to 3 hours. The same type of reaction occurred with Nalline as in the standard withdrawal group, but it was much more profound and fulminating.

Observations on monkey behavior during control periods, during addiction, during control withdrawals, and during postoperative withdrawals were made by only one experienced observer throughout the entire series. Charts on each animal were kept, recording individual preoperative and postoperative characteristics of withdrawal (Tables 2 and 3).

Operations. The operative procedures done to determine the effect on the withdrawal syndrome are sequentially illustrated on the graph in Table 1. The operations were divided into four main groups: cingulumotomy, ablation of area 24, frontal lobectomy, and the control group of operations as illustrated.

Cingulumotomy was performed by making electrolytic lesions in the cingulum with insulated nichrome electrodes, 0.5 mm. in diameter, placed by stereotaxic methods (Fig. 1A). In all cases, 5 lesions were made in the cingulum, starting just posterior to the genu of the corpus callosum in the sagittal plane, 3 mm. apart anteroposteriorly, and 3 mm. from the midline (Fig. 1B). The electrolytic lesions were made with the Grass Stimulator, Model 3-C, using D.C. current, 5 mA. with variable voltage (8 to 12 V.) for 30 sec. The electrodes were introduced through a trephine opening in the skull and appropriate small dural holes produced by electrocautery.

Ablations of area 24 were carried out using the standard subpial suction

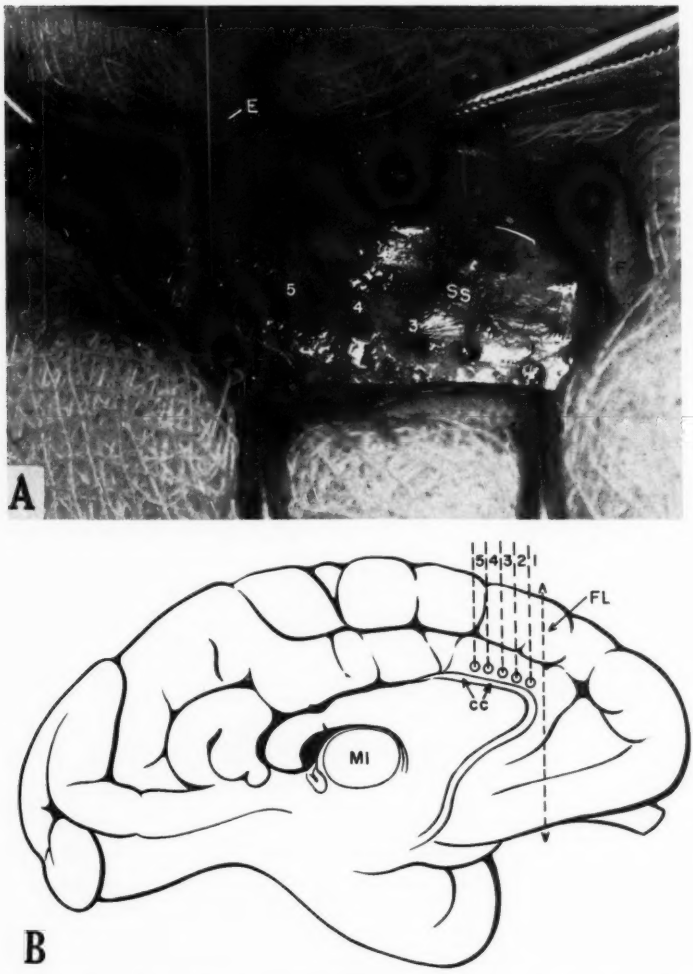


FIG. 1. Technique of cingulumotomy. (A) Operative exposure, midline frontal craniectomy. F—frontal skull. SS—sagittal sinus. E—insulated stereotaxic electrode. 1,2,3,4,5—sites of dural perforations to introduce electrode into cingulum.

(B) Diagrammatic sagittal section of monkey brain to demonstrate location of lesions of cingulum. CC—corpus callosum. FL—line of amputation in frontal lobectomies.

technique for removal of the cortex of area 24, leaving the underlying white fiber tracts of the cingulum intact as far as this was possible. A bifrontal craniotomy was utilized with the dural flap elevated from the medial frontal lobe though bridging veins to the sagittal sinus had to be sacrificed in all cases to obtain lateral retraction and visualization. The extent of the sub-

pial resection was sufficient in all cases to include all of area 24 as described by Ward.[33] The minute landmarks essential in effecting this were surprisingly constant (Fig. 2).

In 1 control animal (cm3), only the exposure of area 24 was carried out. The operative procedure was identical in all respects to the cingulate resections, except that no cortex was resected.

Bilateral frontal lobectomy was done in a single-stage operation through a wide bifrontal craniotomy exposure. The frontal lobe was amputated at the level of the genu of the corpus callosum. This guillotine-type lobectomy was accomplished by using the suction-cautery technique with minimal

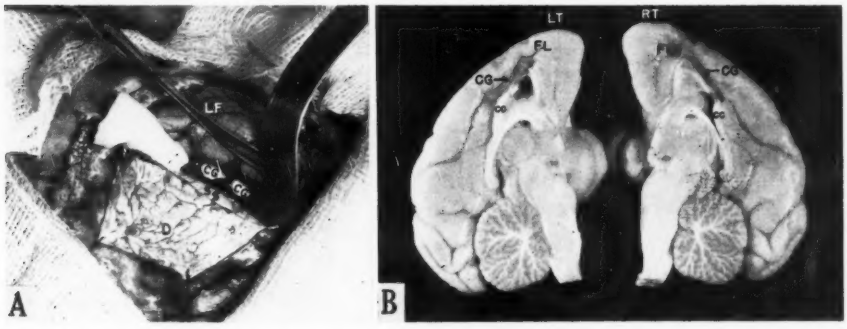


FIG. 2. Resections of cingulate gyrus (area 24). (A) Operative exposure for bilateral resection through bifrontal craniotomy. LF—left frontal lobe. CG—area of resected cingulate gyrus. SS—sagittal sinus. D—reflected dural flap.

(B) Postmortem specimen of brain, bilateral resection of cingulate gyrus. LT, RT—left and right hemispheres; FL—frontal pole; CG—scar over resected cingulate gyrus. CC—corpus callosum.

loss of blood (Fig. 3). In all 3 cases, the areas of the frontal lobe removed included: anterior area 24, anterior area 6, area 8, posterior area 46, areas 45, 44, 11, 9, 10, and 53, as well as anterior area 32.

The control operation for the frontal lobectomies was massive loss of cerebral tissue from a bilateral occipital lobectomy. The operative procedure was similar in detail and extent to the frontal lobectomies but involved the occipital lobes.

Standard sterile neurosurgical technique was used in all operations. The anesthesia was intravenous Pentothal sodium in 2.5 per cent solution, used only in sufficient quantities to obtain adequate anesthesia for each animal. In this way, postoperative narcosis was minimized.

Immediately following all operations, standard or Nalline-induced withdrawal was precipitated and close observations were made comparing the preoperative and postoperative characteristics of withdrawal of that particular animal. Prior to any further operation, the animal operated upon was re-addicted and 2 weeks later put through a similar withdrawal. These two withdrawal syndromes were compared with each other to determine

the persistence of the effect of the operation upon the preoperative withdrawal syndrome.

Anatomical and Histological Control. When the animal was sacrificed, the brain was fixed *in situ* by using intracardiac saline followed by 10 per cent formalin. Following removal of the brain, all gross lesions were photographed and the extent of the lesions was determined by comparison with standard maps of the monkey brain. Serial microscopic sections were made of the cingulum to include all lesions. Alternate sections were stained with Weil or Nissl stain and the extent of the lesions of the cingulum was determined microscopically.

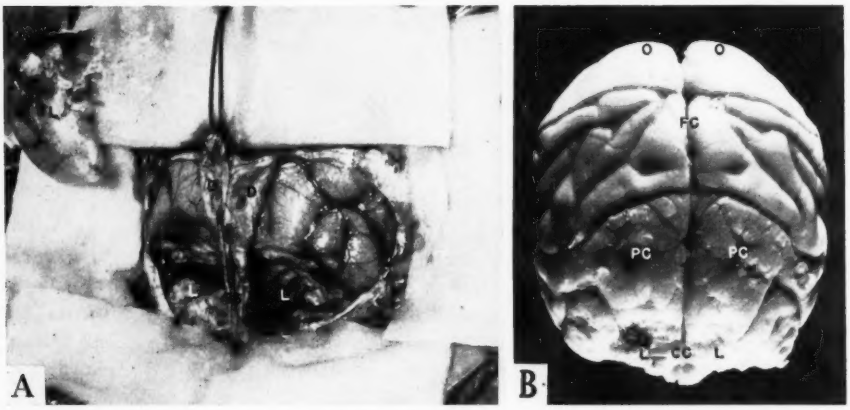


FIG. 3. Frontal lobectomy. (A) Operative exposure for bilateral lobectomy through bifrontal craniotomy. SS—sagittal sinus. L—site of resected frontal lobe. D—reflected dural flaps. FL—frontal lobe.

(B) Postmortem specimen, bilateral frontal lobectomy. L—site of frontal resection. CC—genu of corpus callosum. PC—precentral dimple. FC—falx cerebri. O—occipital poles.

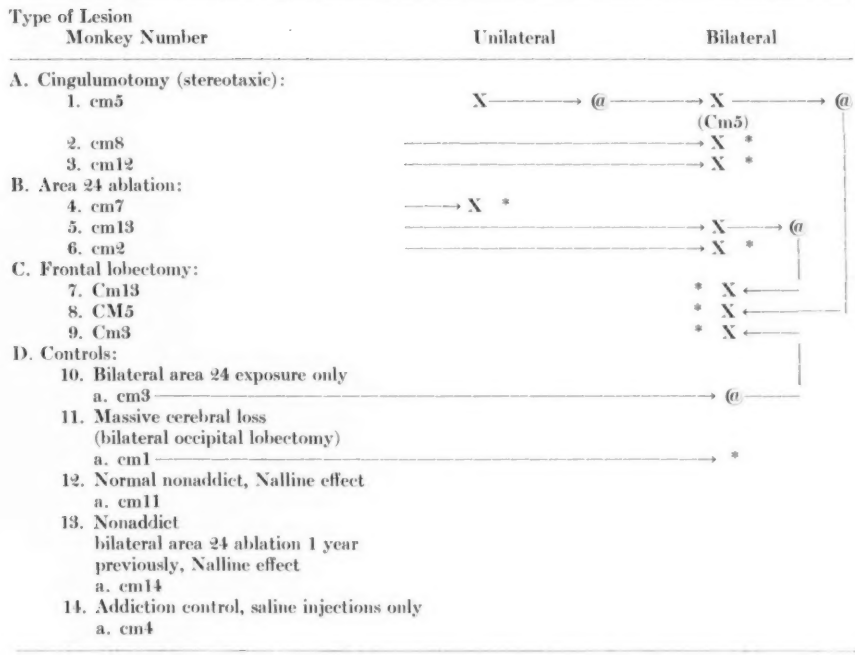
RESULTS

Approximately 2 weeks after the morphine injections were started, the monkeys receiving morphine began to show withdrawal signs between injections. These mild withdrawal signs were subsequently controlled by increasing the frequency of the injections. At no time did any animal show any sign indicative of craving for or interest in the morphine injections *per se*.

The control animals (Table 1) showed no significant changes. This group included a monkey receiving saline injections as a control for the mode of drug administration, a nonaddicted monkey not operated upon receiving Nalline as a control on the direct effects of this drug, and a nonaddicted monkey operated upon (a bilateral area 24 ablation done 1 year previously) receiving Nalline as a control on the direct effects of the drug in an animal after operation.

TABLE 1

Outline of experimental progression



* Animal sacrificed.

@ At least a 3-week interval at this point for controlled withdrawals and re-addiction.

The two forms of withdrawal used, standard and Nalline-induced, did not show characteristics comparable in degree. The results of these two methods are therefore recorded separately in Tables 2 and 3. In Table 2, in each case only those withdrawal characteristics are rated or evaluated that were observed in all the animals in this group. In Table 3, only those characteristics of Nalline-induced withdrawal were rated that were present in all animals in this group. In each tabulation, the responses were those responses felt to be under the volitional control of the animal, whereas somatic responses were presumed to be nonvolitional autonomic phenomena. Such a classification must be recognized as probably arbitrary under these experimental conditions. In both groups, a number of other characteristics of withdrawal[16,29,30] were also present in some of the animals. These were not recorded because no animal-to-animal comparison was possible.

Each withdrawal characteristic in the individual animal was rated 0, 1+, 2+ or 3+ (Tables 2 and 3). Zero indicated no change from the normal behavior pattern of that animal, and 3+ indicated the maximum effect in

TABLE 2

Results of standard withdrawal

Experimental Animal*	Psychic						Somatic				Averages	Withdrawal-Effect Index
	Increased Irritability	Increased Aggression	Tense, Hunched Posture	Grimacing	Capture Vocalizing	Anguished Facies	Piloerection	Tremor, Jerking	Hyperemia, Conjunct.	Diarrhea		Preop. Av. minus Postop. av.
1. em2 preop.	+++	+++	+++	++	+++	++	+++	++	+++	+++	2.7	2.2
postop.	+	+	0	0	+	0	0	+	0	+	0.5	
2. Cm3 preop.	+++	++	+++	++	+++	++	++	+++	++	+++	2.5	2.2
postop.	+	+	0	0	+	0	0	0	0	0	0.3	
3. em1 preop.	+++	0	+++	+++	++	+++	+++	++	+++	++	2.4	−0.4
postop.	+++	+++	+++	+++	++	+++	+++	++	+++	+++	2.8	
4. em3 preop.	+++	++	+++	++	+++	++	++	+++	++	+++	2.5	0
postop.	+++	++	+++	++	+++	++	++	+++	++	+++	2.5	

* Animal designations: em-1st operation; Cm-2nd operation.

this category seen within the group. One+ and 2+ ratings were gradated between these extremes. Each characteristic of the withdrawal syndrome in a given animal was rated for preoperative as well as postoperative withdrawals and the numerical average for the eight or ten individual characteristics of the preoperative and the postoperative syndrome was recorded. The "withdrawal-effect index" represents the decrease in the averaged postoperative responses from the averaged preoperative responses. Therefore, a high index indicated a greater alleviation of the withdrawal signs and symptoms.

TABLE 3

Nalline-induced withdrawal results

Experimental Animal*	Psychic				Somatic				Averages	Withdrawal Index
	Sham Rage, No Fleeing	Automatic Behavior, Searching	Erratic Exhausting, Struggle	Food Rejection	Hyperpnea	Shivering, Rigidity	Piloerection	Salivation, Rhinorrhea, Lacrimation		
5. em7 preop.	+++	+++	++	+++	+++	+++	++	+++	2.7	1.4
postop.	++	+	+	0	++	++	+	+	1.3	
6. em13 preop.	++	+++	+++	+++	+++	+++	+++	+++	2.9	1.9
postop.	0	0	+	0	+	++	++	++	1.0	
7. em5 preop.	+++	++	+++	+++	+++	+++	++	+++	2.8	1.2
postop.	++	+	++	+	+	++	++	++	1.0	
8. Cm5 preop.	+++	++	+++	+++	+++	+++	++	+++	2.8	0.9
postop.	+++	++	++	+++	+	++	++	0	1.9	
9. CM5 preop.	+++	++	+++	+++	+++	+++	++	+++	2.8	2.5
postop.	0	0	0	+	0	0	0	+	0.3	
10. em8 preop.	++	+++	+++	+++	+++	++	++	++	2.8	2.2
postop.	0	0	+	+	++	+	0	0	0.6	
11. em12 preop.	+++	+++	+++	+++	++	++	++	+++	2.6	1.4
postop.	+	++	0	0	++	+	++	++	1.2	
12. Cm13 preop.	++	+++	+++	+++	+++	+++	+++	+++	2.9	2.3
postop.	0	0	0	0	0	+	++	++	0.6	
13. em2 1 yr. postop.	0	0	0	0	+	++	++	++	0.9	1.9†

* Animal designations: em = 1st operation; Cm = 2nd operation; CM = 3rd operation.
† Effect calculated using preop. effect averages in series.

Table 4 shows that the individual "withdrawal-effect index" for bilateral lobectomy ranged from 2.2 to 2.5, for bilateral resection of cingulate gyrus from 1.9 to 2.2, and for bilateral cingulumotomy from 1.4 to 2.2. The qualitative effect of resection of the cingulate gyrus and cingulumotomy approximated more closely the effect of frontal lobectomy than these quantitative estimates might indicate.

Postmortem studies showed that gross inaccuracies in stereotaxic place-

TABLE 4

Summary of operative results on withdrawal index

Operation Performed	Withdrawal-Effect Index
1. Bilateral frontal lobectomy:	
a. Cm13	2.3
b. CM5	2.5
c. Cm3	2.2
2. Bilateral area 24 ablation:	
a. cm13	1.9
b. cm2	2.2
c. cm2 (re-addicted 1 year postop.)	es 1.9
3. Bilateral cingulumotomy:	
a. cm8	2.2
b. cm12	1.4
c. Cm5	0.9*
4. Unilateral area 24 ablation:	
a. cm7	1.4
5. Unilateral cingulumotomy:	
a. cm5	1.2 (temporary only)
6. Control animals:	
a. Bilateral occipital lobectomy:	
1) cm1	0.2
b. Area 24 exposure only, bilateral:	
1) cm3	0.0

* Ineffectual lesions—see Table 5.

ment of lesions of the cingulum correlated well with the poor effect on the withdrawal syndrome. In 2 of the 3 animals with bilateral cingulumotomy, 75 per cent or more of the cingulum was destroyed as estimated by serial histologic study. Both of these animals showed a significant index of 1.4 and 2.2 (Table 4). The animal who proved to have an inaccurate operation showed an index of only 0.9. The withdrawal-effect index thereby correlated well with the degree of destruction of the cingulum. Table 4 also shows that with unilateral resection of the cingulate gyrus the index was 1.6 and with unilateral cingulumotomy the index was 1.2, both significantly below that of animals with comparable bilateral lesions. Both operative control animals (occipital lobectomy and exposure of cingulate gyrus) had very low indices.

Postmortem anatomical studies verified that the resections of anterior cingulate gyrus were done completely and also showed that the underlying cingulum was damaged grossly (Fig. 4). Postmortem studies likewise verified the extent of the frontal lobectomies.

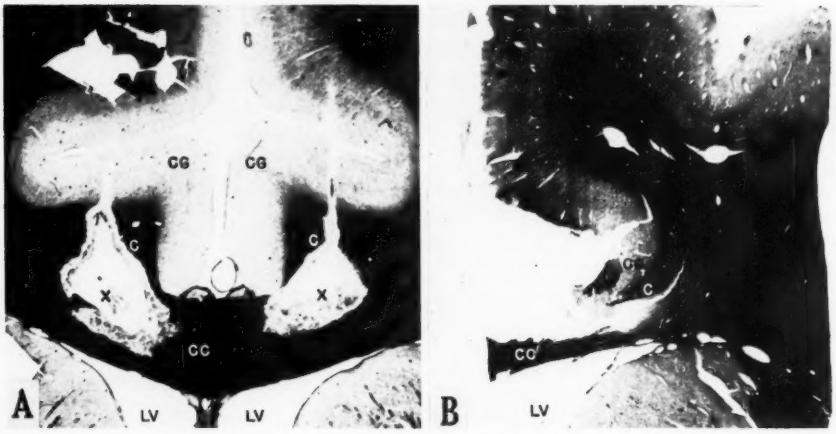


FIG. 4. (A) Photomicrograph of coronal section demonstrating histologic extent of lesion in bilateral cingulumotomy (Weil stain). CG—cingulate gyrus cortex. C—fiber tracts under cingulate gyrus. X—electrolytic lesions destroying major portions of cingulum bilaterally. CC—corpus callosum. LV—lateral ventricles.

(B) Photomicrograph of coronal section demonstrating histologic extent of resection of left cingulate gyrus (Weil stain). CC—corpus callosum. CG—remnant of cingulate gyrus cortex in sulcus. C—largely destroyed cingulum. LV—left lateral ventricle.

One animal (Tables 2 and 3, cm2) who had been used in the standard withdrawal group to test the effects of bilateral resection of anterior cingulate gyrus was re-addicted 1 year later. Withdrawal precipitated by Nalline demonstrated that cingulate resection still attenuated the withdrawal syndrome and resulted in an excellent withdrawal-effect index of 1.9. The latter was derived by comparing the animal's Nalline-withdrawal behavior with his previous preoperative spontaneous withdrawal activity and with the behavior of the other addicted animals in Nalline-precipitated withdrawal.

DISCUSSION

Standard withdrawal and Nalline-induced withdrawal were both used in this study. The only significant difference in these withdrawals was the shorter duration and more intense signs produced by Nalline. This method was just as reliable though with danger to the animal since a severe withdrawal pointing toward a fatality could not be modified by morphine injections as in the standard withdrawals. Nalline produces a nonreversible withdrawal in addicts as previously documented.[37–39] These two methods of withdrawal were used interchangeably in the preoperative and postoperative studies with no discernible difference in the results though emphasis on certain aspects of each withdrawal varied in the two groups (Tables 2 and 3).

The division of signs and symptoms of withdrawal into "psychic" and "somatic" as done in Tables 2 and 3 is largely artificial. Such a separation

depends for accuracy on direct communication with the subject to assess the psychic component. Such was not the case in the experiments. Therefore, these experiments cannot determine whether frontal lobe operations attenuate the morphine-withdrawal syndrome by an effect on the psychic component or the somatic component of the withdrawal. A change in concept in this regard was mandatory early in the project since such a classification was not reliable with this technique.

The "withdrawal-effect index" (Table 4) does show that the total effect on withdrawal is significant in all three operations if done bilaterally. Unilateral ablation of the cingulate gyrus and unilateral cingulumotomy do modify the withdrawal syndrome but are not as effective as the bilateral procedures (Table 4).

The surprising effectiveness of simple interruption of the cingulum behind the genu of the corpus callosum again emphasizes the role of the limbic system in autonomic phenomena and emotional behavior. In early withdrawal of morphine, an experimentally produced state of autonomic hyperactivity and behavioral or emotional hyperreactivity is present. In view of the accumulating knowledge concerning the limbic system,[1,2,5,8,11,13,20,24] it was reasonable to expect alleviation of this state through interference with normal function of the limbic system by blocking or altering cortical afferent pathways into the system. This was accomplished by stereotaxic cingulumotomy and the attenuation of the morphine-withdrawal syndrome was striking even though only incomplete severance of the cingulum was achieved.

The effectiveness of cingulumotomy forces us to consider whether disruption of the cingulum is the essential and critical factor in the alleviation of symptoms of withdrawal obtained in all of these experiments. Whereas the origin of the fibers making up the cingulum is not widely known, sufficient evidence is available to show that medial frontal, possibly orbitofrontal, and anterior cingulate cortex send fibers into the cingulum for posterior transmission by long and short multisynaptic pathways to posterior areas 24 and 23, and thence toward the hippocampus.[2] There is likewise evidence of possible transmission from hippocampus to cingulate gyrus through the cingulum.[13] However, the exact physiology and anatomy of these relationships in the cingulum have not been completely delineated.

On a quantitative basis, the results indicate that massive frontal lobectomy was slightly more effective than cingulate resection and cingulumotomy. On a quantitative basis, however, the effects of the three procedures were very similar. A destructive lesion common to all three operations would explain this similarity. The only such lesion was in the cingulum. Resection of the cingulate gyrus probably always damages the underlying cingulum (Fig. 4) and frontal lobectomy excises almost all the frontal cortex feeding into the cingulum (Figs. 1B and 3).

As indicated by the "withdrawal index," the frontal lobectomy was superior in its quantitative modifications of symptoms of withdrawal to both

the cingulate resection and cingulumotomy. Lobectomy was done at the genu of the corpus callosum and thereby, in effect, caused a complete cingulumotomy by removing all frontal cortical areas known to contribute to the cingulum, including the anterior cingulate gyrus. On the other hand, stereotaxic cingulumotomy produced a maximum of only 80 to 85 per cent bilateral transection of the cingulum, and the cingulate resection removed all of anterior area 24 as well as partially damaging the cingulum. Therefore, it is reasonable to expect a greater withdrawal-effect index by lobectomy since it achieved a greater effect on the limbic system than the other two procedures. Possibly a stereotaxic cingulumotomy which completely transected the cingulum would modify the morphine-withdrawal syndrome to as great a degree as frontal lobectomy, but we at present have incomplete evidence in this regard.

Table 5 shows that none of the cingulumotomies achieved complete

TABLE 5

Anatomical results of cingulum lesions

Experimental Animal	Per Cent Cingulum Destroyed	
	Rt.	Lt.
cm5	0	50
cm8	75	75
cm12	80	85
Cm5	10	50

severance of the cingulum, the maximum being 80 to 85 per cent in animal cm12. The degree of destruction was estimated by measurements of the cross-sections of the cingulum studied in serial section throughout the length of the cingulum. Five lesions were made in each cingulum in the anteroposterior extent (Fig. 1B) to improve the chances of total transection of the cingulum. In some instances, the medially placed, large fibers (presumed to originate from the anterior cingulate gyrus) were not destroyed, whereas the laterally placed, small fibers (presumed to carry impulses from medial and orbital frontal cortex[1]) were completely ablated. No differentiation in effectiveness of the lesions of the cingulum was possible on the basis of the type of fibers involved nor on the basis of the origin of the fibers. Furthermore, destruction of at least 75 per cent of the fibers of the cingulum on one side was necessary to detect an effect on symptoms of withdrawal.

Clinical evidence concerning the effect of resection of area 24 on agitated emotionally disturbed patients[18,19] can be interpreted as supporting the results of cingulumotomy obtained in this experimental work. The tranquilizing effect thus achieved clinically is similar in many ways to the effect of cingulumotomy on the hyperirritability, hyperreactive aspect of experimental morphine withdrawal. As described clinically, resection of area 24[18,19] must

cause significant ablation of the underlying cingulum. The clinical effect may thereby be the result of an effective cingulumotomy. Ward[32] and Livingston[19] likewise noted that prefrontal lobotomy following anterior cingulate undercutting resulted in no significant change, thereby possibly implicating damage to the cingulum at the time of cingulate resection.

The role of the cingulum in emotional behavior and autonomic hyperreactivity is not completely clear. However, Papez' original concept in 1937[24] was that the cingulum served as an association fasciculus between autonomic centers of medial frontal lobe and the hippocampal formation, and thus subserved the functions of both these areas. Recent experimental data[1,2,4,9,11,13] indicate a relatively close anatomical and physiological relationship between portions of the hippocampal formation and fibers in the cingulum. Though only partial delineation of the frontal cortical areas feeding into the cingulum has been carried out there is presumptive evidence that integrating mechanisms may exist from frontal cortex via the cingulum to the limbic system. This cortical influence, probably in the emotional sphere, may serve to initiate or perpetuate autonomic activity of the limbic system under usual conditions. Thus, optimum and advantageous responses for the organism as a whole are achieved. Withdrawal of morphine from an addict, however, may result in a rapid increase in the facilitative effect of frontal cortex on the limbic system, thereby disrupting the normal balanced relationship. Such a high degree of autonomic hyperactivity and hyperreactivity results that existence itself is endangered. Destruction of pathways of the cingulum under these conditions would then destroy or modify the facilitative effect of frontal cortex on activity of the limbic system, thereby markedly reducing the autonomic effects of withdrawal mediated through the limbic system or "visceral brain." In this way, the entire syndrome of morphine withdrawal, including both the "somatic" and "psychic" factors previously observed, would be significantly modified by interruption of the cingulum through cingulumotomy, resection of the cingulate gyrus, and frontal lobectomy, as observed in this series of experiments.

Further support to this thesis is given by the results in the one animal that had had a resection of the cingulate gyrus 1 year previously during a cycle of observations on standard morphine withdrawal. In this animal (cm2) the modification of symptoms of withdrawal was still striking (Table 3). This effectively rules out "diaschisis" or cerebral shock as a major factor in modification of the withdrawal syndrome by frontal lobe lesions. This could mean that the cingulumotomy is effective on a chronic basis in preventing facilitation of autonomic hyperactivity of the limbic system in morphine withdrawal by blocking a part of its integrating mechanism.

Cingulumotomy as described here has been done clinically only in a limited number of cases. In all instances, the patients suffered from pain which was felt to be primarily on a psychogenic or emotional basis. The results thus far are very good but too limited in number to warrant further discussion.

SUMMARY AND CONCLUSIONS

1. Modification of the effects of morphine withdrawal by selective frontal lobe lesions and control lesions has been studied in monkeys. Repeated careful observations of each monkey's basic activity and reactivity during preoperative withdrawal of morphine are compared with the same criteria postoperatively. A "withdrawal-effect index" is calculated for each monkey from these data. The reliability of this index is well supported by the results in the control animals.

2. The selective frontal lobe lesions studied for their effects on morphine withdrawal were stereotaxic cingulumotomy, resection of the cingulate gyrus, and frontal lobectomy. The control procedures were occipital lobectomy and mock operations.

3. The effects of morphine withdrawal in addicted monkeys could not be divided into the "psychic" (purposive) and "somatic" (nonpurposive) components as previously classified.

4. The syndrome of experimental morphine withdrawal in the monkey appears to be a state of hyperactivity of the autonomic system which, if unaltered, can lead to death. Such effects presumably are mediated through the limbic lobe or "visceral brain." Therefore this experimental syndrome may be useful as an indicator in the study of the function of the limbic system as well as systems integrating with the limbic system, such as the frontal lobe.

5. The qualitative modification of the effects of withdrawal was strikingly similar after all three frontal lobe lesions. The quantitative modification as measured by the "withdrawal-effect index" showed that frontal lobectomy was slightly superior to cingulumotomy and to resection of the cingulate gyrus. The control operations, including massive occipital lobectomy, had no effect on the syndrome of withdrawal.

6. Modification of the symptoms of withdrawal persisted up to 1 year. The unilateral frontal lesions caused a significant modification, but bilateral lesions were much more effective.

7. Since the effects of morphine withdrawal modified by the frontal lesions were so similar, since the only lesion common to all three operations was disruption of the cingulum, and since these results correlate well with recently reported observations concerning function of the cingulum, it is postulated that interruption of the cingulum is the critical physiologic lesion producing modification of the autonomic hyperactivity in morphine withdrawal.

8. The role of the cingulum as an association fasciculus from frontal lobe to the limbic system is discussed. A thesis is proposed to explain how the autonomic hyperactivity of morphine withdrawal is modified by cingulumotomy through the loss of emotional facilitation of the limbic system from the frontal lobe. However, no claim is made as regards specific delineation of function or structure of the ill-defined tract known as the cingulum.

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DISCUSSION

Dr. Kenneth E. Livingston: For more than 30 years the monkey has served as a reliable indicator for the pharmacological investigation of narcotic compounds. The monkey's reaction to morphine withdrawal after addiction is strikingly similar to that seen in humans and in both the monkey and human addicts the concept of "tissue dependency" seemed well established—that is, the severe visceral disturbances and even death following abrupt withdrawal of the narcotic were ascribed to physiological alterations in peripheral tissues.

For the past 10 years this concept of "tissue dependency" as an explanation for the withdrawal crisis has been *untenable*. Clinical experience with lobotomy for pain has demonstrated that the profound visceral disturbances expected on withdrawal do *not* occur following frontal lobotomy.

This paper is, I believe, the first experimental analysis of this striking phenomenon. Dr. Foltz and Dr. White have provided an indicator against which the effectiveness of various frontal lobe lesions can be compared experimentally. This represents a great step forward in the investigation of the frontal lobe, and many important extensions of their present study come immediately to mind.

It is appropriate that they should direct their initial attention to the cingulate area since this is one of two strong visceral effector regions of the prefrontal cortex. Nevertheless, it is startling to learn that lesions of such anatomically limited extent as those of the cingulum bundle can reduce or abolish disturbances *so* widespread and *so* widely mediated through the nervous system.

If a restricted frontal lobe lesion can produce such profound change in visceral response, it is tempting to speculate whether other clinical syndromes in which visceral function is seriously disordered may also be influenced by cingulate lesions. This paper may serve as a stimulus to extend the few clinical studies already undertaken in this field.

In the present investigation suppression of the withdrawal syndrome appeared undiminished a year after the cingulate resection. This observation plus the clinical experience that lobotomized patients seem resistant to re-addiction suggest the possibility that cingulate lesions may be useful in the management of primary addiction.

To what extent can the relationship between the effectiveness of extensive lobectomy and the restricted cingulate lesions reported here, be transposed with validity to the problems of treatment in the psychoneuroses and psychoses? This question is, of course, presently unanswerable. However, since visceral function is inseparable from emotional expression and behavior, a lesion capable of exerting such marked effect on disturbed visceral function might

well be expected also to *modify* more complex disorders of emotion and behavior. The authors state that they have produced cingulumotomy lesions in a few patients. We have also produced lesions in this area without difficulty in over 100 patients, and we feel that further clinical investigation in the light of their experimental observations is entirely feasible.

In closing, I feel that we will in the future look back on this paper as a landmark in our investigation of frontal lobe function. I offer my hearty congratulations to Dr. Foltz and Dr. White and include in my appreciation their silent but esteemed collaborator Arthur Ward.

DR. ORLANDO J. ANDY: The authors of this very fine paper have postulated that the beneficial effects observed in their animals were primarily the result of the interruption of the cingulum. I would like to present some experimental data which tend to question this postulate.

[Slide] This demonstrates the gross anatomical relationships between the cingulate areas and the hippocampal system. Anatomically the cingulum is a fiber pathway serving to connect the cingulate and anterior medial frontal areas with the hippocampal system. In order to evaluate the functional importance of this anatomical connection, the behavioral and electrical changes occurring during seizures induced in the cingulate gyrus and the hippocampal system were compared. The influence of one upon the other was also noted.

[Slide] Seizures were induced in the supercallosal portion of the cingulate gyrus and in the subiculum alternately every 2 minutes. As you will note, the hippocampal seizure discharge became longer as the cingulate after-discharge became shorter. This apparent influence of one structure upon the other, however, could not be substantiated by other experiments, such as the following.

[Slide] In this experiment a hippocampal discharge is induced every 4 minutes preceded by a cingulate after-discharge 1 minute before each of the hippocampal-induced stimulations. It is evident that the cingulate discharge has neither a tendency to prolong nor curtail the duration of the hippocampal discharge.

[Slide] A series of individually induced hippocampal discharges are compared with a series of discharges in which a cingulate stimulation was introduced during the course of each hippocampal discharge. Again, the cingulate activity had no apparent influence upon the duration of the hippocampal seizure.

[Slide] This illustrates a cingulate discharge which propagates very well to the right pulvinar nucleus but not to the hippocampal system which is represented by the mammillary body and septal area. This reveals that the cingulate gyrus possesses pathways for propagation of electrical impulse which may be functionally much more significant and active than that represented by the cingulum.

[Slide] However, with suprathreshold stimulation of the cingulate gyrus a very well self-sustained hippocampal discharge can be induced, as demonstrated in this slide. It must be emphasized, however, that this activity was induced with a stimulation of 6 volts, which represents a strength 2 to 3 times threshold.

[Slide] In this experiment, 84 cingulate gyrus seizures were induced consecutively. Out of the 84 there were only 7 that resulted in activation of a self-sustained hippocampal discharge. If one were to assume that the cingulum provided a functionally very active pathway to the hippocampal system, repeated stimulations of the cingulate gyrus should certainly induce a higher percentage of hippocampal discharges.

[Slide] There is a propagation of 7 to 8 per sec. activity from the subiculum to the anterior cingulate region but not to the posterior cingulate. A few authors believe that fibers in the cingulum may go in two directions. If this activity were conducted by the cingulum, it should have been present in the posterior cingulate also. Another point worth while illustrating on this slide concerns sleep spindles which are present in the control run but completely absent during the subiculum after-discharge. If this were a cingulate after-discharge, the sleep spindles would definitely continue and not disappear from the cortex. Thus, we have another predominant difference between the cingulate and hippocampal systems.

Another approach in studying this problem was to compare the blood pressure response during a discharge in each of the two systems.

[Slide] There is a very slight, 5 mm. or so, but definite rise in blood pressure following stimulation of the hippocampus. Although a rise may not occur there is never a drop in blood pressure.

[Slide] Precallosal cingulate stimulation induces a slight but very definite drop in blood pressure. Supercallosal cingulate stimulation, however, does not alter the blood pressure level. This difference certainly discounts the cingulum, which is common to both, as having anything to do with the observed effects. Of further significance is the fact that an electrical discharge obtained from the precallosal cingulate does not appear to propagate to the more posteriorly located supercallosal cingulate. In contrast, the more posterior cingulate discharge definitely does propagate to the more anteriorly located point.

Behaviorly there is a marked difference between the cingulate and hippocampal system discharges. For example, a cat will in most instances not attack a mouse during a hippocampal discharge; whereas it will definitely attack a mouse during a cingulate seizure. A ferocious cat which attacks the investigator can be made docile by a hippocampal-induced seizure. In contrast, a cingulate gyrus discharge does not alter a cat's ferociousness and aggressiveness.

In conclusion, I am inclined to believe that the cingulate gyrus activity has very little direct influence by way of the cingulum upon the function of the hippocampal system. I should like to encourage the authors of this most interesting and provocative paper to repeat their studies in animals having small transverse cuts placed in varying planes throughout the course of the supercallosal portion of the cingulum.

Dr. William B. Scoville: I wish to congratulate Drs. Foltz and White on their clinical and animal studies on the relief of drug addiction in psychoneurotic patients. Lobotomy studies confirm their results. In fact, most psychosurgeons who have developed selective lobotomies, both within the deep white matter in the medial inferior quadrants as well as cortical undercutting and cortical resections of various areas of the prefrontal lobe, have observed a dramatic relief from drug addiction following operation, regardless of the location of the lobotomy. Undercutting of the cortex of the superior convexity, of the orbital surface, and of the anterior cingulate gyrus, performed in the Hartford Hospital, has given such relief. Hence, this speaker questions any specificity of the cingulate gyrus as affecting addiction unless one postulates that all frontal lobe cortical connections must pass through the cingulum. The speaker prefers a simpler explanation, and that is that any type of fractional prefrontal lobotomy causes some blunting of higher sensitivities, especially a blunting of the memory and anticipation of pain, together with anxiety. Such blunting relieves the craving of addiction. Cingulumotomy may accomplish such results not by any specificity but rather by interruption of the connections from the entire prefrontal cortex which concentrate and converge into the medial inferior bundle and cross very close to the connections of the anterior cingulate gyrus and cingulum. Hence, even fractional interruption in the region of these concentrated fibers may result in a quite remarkable effect on personality, anxiety and addiction.

Dr. Russell Meyers: I do not often find it necessary to disagree on neurophysiologic matters with our colleagues from Seattle, but in the present case I confess to some disquietude regarding the logic apparently used by the essayists in their effort to interpret the findings of their experiments. In principle, they appear to have fallen into what I have elsewhere called the fallacy of the common denominator. Let it be said that this is not an unusual logical aberration for investigators in the biologic and medical sciences to exhibit. I have invited attention to it during the past few years in mounting formal criticisms of certain papers endeavoring to localize "the center of consciousness" (*Arch Neurol. Psychiat., Chicago,* 1951, *65:* 659–671) and seeking to explicate the "functions" of certain structures of the basal ganglia

(*Neurology*, 1953, *3:* 627–655) and periaqueductal gray matter (*Trans. Amer. neurol. Ass.*, 1954, 121–123).

Let us quickly examine the principles involved by making use of what the mathematicians would call reduction to a simple form. We shall assume a naive investigator sets out to identify "the function" of the liver. He begins by observing four lobes: right, left, caudate and quadrate. He first extirpates the right lobe of the liver in a small series of animals and observes no deficit in biologic economy. In a second series he extirpates the left and in a third, the quadrate lobe. In no case does he observe a biologic deficit. Thus far, no "function" can be assigned to any of these portions of the liver.

Our investigator nevertheless resolves to pursue the problem to combined lesions. Let us suppose that for some reason or other he omits to extirpate the caudate lobe *to the complete exclusion* of the other three lobes: perhaps it is technically not feasible to accomplish; or perhaps his research design is merely inept. Whatever the reason, he pushes on with "combined" lesions. In a new series of animals he removes the right and the quadrate lobes and in another the left and the quadrate lobes. No physiologic deficit appears.

It happens (we will suppose) that, while experimental removal of the caudate lobe *alone* is technically infeasible, its removal along with other lobes is easily accomplished. Our investigator now enters upon what he regards as a crucial test. He removes the right, the quadrate *and* the caudate lobes in a new series of animals and now, for the first time, notes a functional disturbance, let us say, a prolonged prothrombin time. In another series, he removes the left, the quadrate *and* the caudate lobes. Again, the deficiency in prothrombin time is found. He now deduces that the function of providing a proper prothrombin time must be imputed to the one common denominator of the series in which a disturbed function is demonstrable, namely the caudate lobe.

This is manifestly not allowable in Aristotelian logic, much less in the modern symbolic logic which is so usefully adaptable to the biologic sciences.

The parallels between our hypothetic illustration and the inferences suggested by Drs. Foltz and White regarding the functional role of a portion of the limbic apparatus should be apparent. I do not believe their inferences compellingly follow. This is not to say that they are necessarily wrong: it may just happen that a proper conclusion was hit upon, even though the steps leading up to it have been faulty. I wish merely to indicate that other, more crucial experiments can and must be implemented before we can agree with the authors.

Dr. E. L. Foltz: We felt we might be misinterpreted and I think this has occurred! I simply would like to read our last statement again, if I may: "No claim is made as regards specific delineation of function or structure of the ill-defined tract known as the cingulum."

ISOTOPE TRANSFER TEST FOR DIAGNOSIS OF VENTRICULOSUBARACHNOIDAL BLOCK

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SINCE the time of Vesalius[8] the term hydrocephalus has been used to designate the excessive accumulation of cerebrospinal fluid in the cranium without reference to the causative factor producing the pathological process. Interestingly enough such a designation is still in vogue, particularly in reference to children. Dorothy Russell[6] has stated the overall problem quite clearly: " . . . the immense variety of pathological lesions productive of hydrocephalus have this single feature in common: all create an obstruction at some point in the pathway of the cerebro-spinal fluid." The classification proposed by her is based on an extensive review of necropsy material and conforms completely with our experience. The responsible pathological factor or factors for ventricular hydrops fall in four categories: malformations of the cerebrospinal axis, secondary to inflammatory diseases, a sequel to cerebral trauma, and in association with tumors. The anatomical locations of the lesions blocking the pathways of the cerebrospinal fluid are: lesions within the lateral ventricles, at the foramina of Monro, within the 3rd ventricle and iter, within or encroaching upon the 4th ventricle or the foramina of Luschka, in the subarachnoid space at the level of the incisura tentorii, partial obliteration of the subarachnoid space of the cerebral hemispheres, and obstruction of the dural venous sinuses. Diagnostic efforts should therefore be directed at a determination of the site of obstruction of the cerebrospinal fluid. Correlation of this with the other clinical features has been helpful in arriving at a logical diagnosis.

Among the supplementary diagnostic procedures that have been employed may be mentioned the phenolsulphonphthalein test of Dandy and Blackfan[3] (reviewed recently by Bering[1]), pneumoencephalography and ventriculography,[2] intraventricular injection of radio-opaque contrast media,[7] modification of Dandy's encephalography and ventriculography,[4] and vertebral angiography.[5] In some instances these procedures, singly or in combination, have established the site of obstruction of the cerebrospinal fluid and the pathological process responsible for the hydrops. Far too frequently after the gamut of diagnostic procedures has been exhausted a precise diagnosis remains obscure. Such circumstances lend stimulus for continued search for a better method of determining the site of block.

During an investigation of the rate of exchange of radioactive human serum albumin across the subarachnoid-vascular barrier in cases of "hydro-

cephalus," it soon became apparent that a nontoxic substance was available which might be useful in the determination of the site of block in the cerebrospinal fluid pathways. Thus a method was found which involved: a simple cerebral ventricular puncture without appreciable alteration of the ventriculosubarachnoidal hydrodynamics, the introduction of a chemically inert radioactive substance, and the identification of the position of this tracer substance by means of an external Geiger-Müller counter. Here then was a method for the study of obstruction to flow within the spaces containing cerebrospinal fluid without side effects. Moreover the procedure offered a means of determining patency of tubes used in ventriculoperitoneal shunts.

METHOD

In the present study, radio-iodinated (I^{131}) human serum albumin (RISA) was introduced into the ventricular system either by puncture of a lateral ventricle through an open fontanelle or a previously made cranial burr hole. The dosage employed was 100 μc. Immediately following injection the patient was placed in the erect position. The detector used was a shielded Anton G-M eye probe. The total counts per minute were obtained along the cerebrospinal axis. The total counts per minute were then plotted versus the inverse square of the distance from the point of injection (I/D^2).

PHYSICAL CONSIDERATIONS

As is well known, the intensity of radiation from a point source is inversely proportional to the square of the distance at which it is measured. This inverse square law of radiation physics is applicable in cases of obstruction in which the source of activity is limited to the ventricular system. If free communication exists between the ventricular system and the spinal subarachnoid space, other factors contribute to the intensity of radiation along the cerebrospinal axis. In addition to being a function of the law, the intensity of radiation is directly proportional to the cross-sectional area of the spinal subarachnoid space under observation, the rate of diffusion of the tracer material, and possibly the effect of the pumping action of the choroid plexus. Therefore in examples in which there is a block between the ventricles and the spinal subarachnoid space, a straight line is obtained when the total counts per minute are plotted against the reciprocal of the square of the distance. If free communication exists in the ventriculosubarachnoidal system, a curve plotted in the same fashion represents a complex function.

RESULTS

Twenty-five unselected patients with clinical evidence of hydrocephalus were submitted to this isotope transfer test. The following 3 case histories are illustrative.

Case 5. KCH #54525. W.J., a 10-month-old male, was admitted to the hospital because of progressive enlargement of the head of 8 months' duration. The circumference at the occipitobregmatic level was 66 cm. The chest measured 45 cm. One

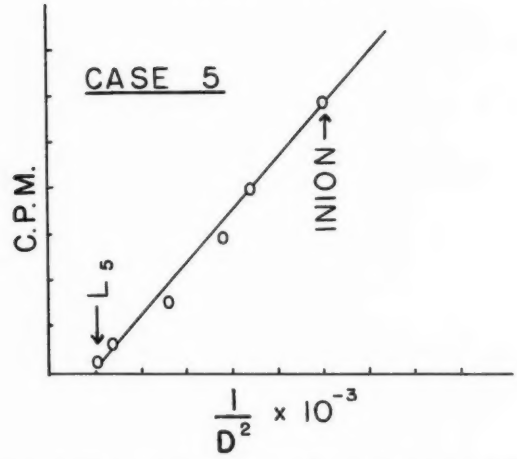

FIG. 1. Curve obtained with ventriculosubarachnoidal block. In Figs. 1–4: C.P.M. = counts per minute; $1/D^2$ = inverse square of distance from point of injection.

hundred μc. of radio-iodinated serum albumin were introduced by injection into the right lateral ventricle through the anterior fontanelle. Measurements were made of the intensity of the radiation along the cerebrospinal axis and plotted as described (Fig. 1).

Comment. Fig. 1 represents a typical plot of isotope transfer in an exam-

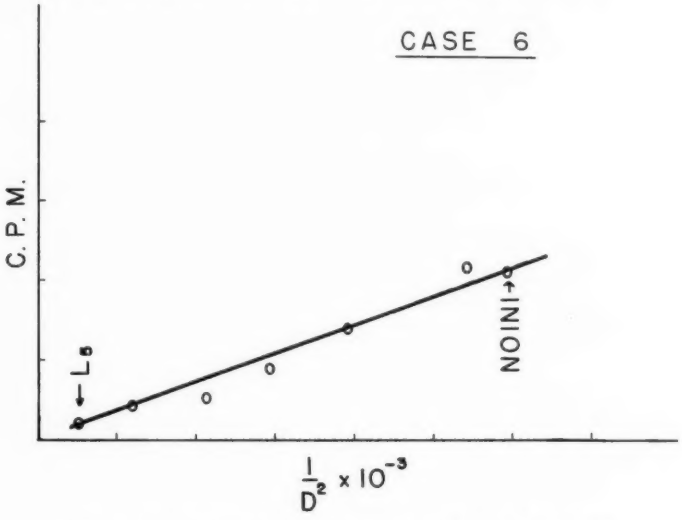

FIG. 2. Measurements along the midline of the head and vertebral column indicate a ventriculosubarachnoidal block.

ple of ventriculosubarachnoidal block. Surgical exploration of the posterior cranial fossa revealed what was considered to be atresia of the foramina of Magendie and Luschka with massive hydrocephalus, including dilatation of the iter and 4th ventricle.

Case 6. B.H. #168600. R.D., a 4-month-old male, was admitted to the hospital because of progressive enlargement of the head. Ventriculography revealed a symmetrically dilated system. A ventriculoperitoneostomy was performed. Following this procedure, the signs of intracranial hypertension subsided, the fontanelle became soft and the circumference of the head remained stationary. One month following the shunting procedure, 100 μc. of radio-iodinated serum albumin were injected into the left lateral ventricle through the anterior fontanelle, and the intensity of radia-

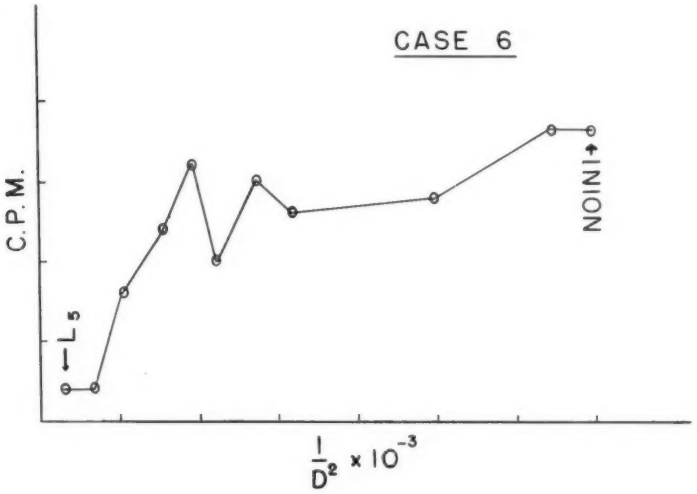

FIG. 3. A complex curve obtained from the same patient as in Fig. 2. However, measurements were obtained over the ventriculoperitoneostomy tube.

tion was measured along the cerebrospinal axis (Fig. 2). Measurements were then made of the intensity of radiation over the shunt tube, and the data were plotted in the same fashion (Fig. 3).

Comment. Fig. 2 indicates an obstruction of the ventricular pathway. The curve in Fig. 3 represents a complex function signifying patency of the shunt tube used for drainage of the ventricular fluid into the greater peritoneal cavity.

Case 9. KCH #48967. C.F., a 45-year-old male, was admitted to the hospital because of difficulty in walking. Pneumoencephalography revealed dilatation of the lateral ventricles. The 4th ventricle was not visualized. Surgical exploration of the posterior cranial fossa revealed no evidence of a mass lesion and patency of the foramina of Magendie and Luschka was verified. On the 10th postoperative day, 100 μc. of radio-iodinated serum albumin were instilled in the right lateral ventricle

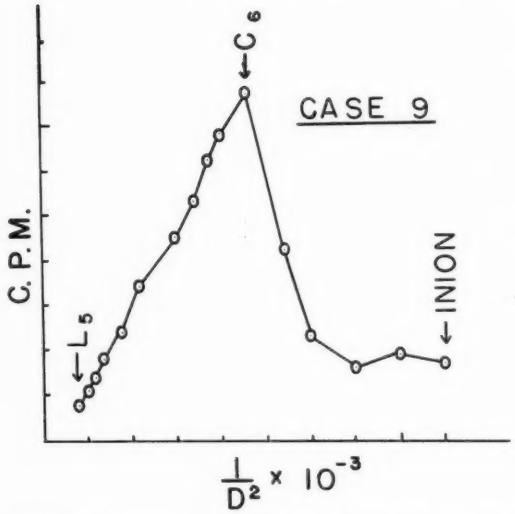

FIG. 4. Complex curve obtained with free flow between the cerebral ventricles and the subarachnoidal space.

through a previously made burr hole. Measurements of intensity of radiation were made along the cerebrospinal axis and the data were plotted (Fig. 4).

Comment. In this case, in which the hydrocephalus was associated with "cerebral atrophy," isotope transfer demonstrated free communication of the ventriculosubarachnoidal pathways. This conclusive information could have been obtained by the isotope transfer test without subjecting the patient to surgical exploration.

DISCUSSION

Twenty-five unselected patients with ventricular hydrops were studied with the isotope transfer method. The accumulated evidence in 13 of these indicated that the hydrops was caused by obstruction of the aqueduct of Sylvius or at the portals of exit for cerebrospinal fluid of the 4th ventricle. In each of the 13 patients it was possible to demonstrate a block between the ventricular and subarachnoidal systems. In only one patient was there a complication following the intraventricular injection of RISA. In this instance, shortly after injection, there was hyperpyrexia which continued for 48 hours. Eight hours after the injection of RISA the ventricular fluid was found to be clear and acellular. In 7 of the 25 cases ventriculoperitoneal shunts had been performed. The shunting tubes became blocked in 6 at variable periods following operation, which was demonstrated by the method under consideration. No patients have been examined upon whom either ventriculoureterostomy or arachnoidureterostomy has been performed.

SUMMARY

In our present state of knowledge concerning the pathogenesis of ventricular hydrops, it would seem justifiable to conclude that the isotope transfer test is the easiest and simplest method of demonstrating a ventriculosubarachnoidal block. In addition the test has been found useful in determining the patency of tubes *in situ* that have been employed as shunts in arachnoidperitoneostomy and ventriculoperitoneostomy.

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CASE REPORTS AND TECHNICAL NOTES

INFUNDIBULOMA

A CASE REPORT WITH A BRIEF REVIEW OF THE LITERATURE

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The purpose of this paper is to report the fifth case of infundibuloma recorded in the literature since 1942 when Globus[2] first studied and described a hitherto unknown tumour of the infundibular region. Prior to this date, these neoplasms may have been placed in groups to which they bore some resemblance, but the work of Globus showed they belonged to a category which was quite distinct and previously unrecognised. In the case presented below the patient was the youngest of any that has so far been reported and we feel that the tumour was present since birth.

REVIEW OF THE LITERATURE

Of the many tumours in the region of the 3rd ventricle, which have been exhaustively studied, the infundibuloma first described by Globus[2] presents certain characteristic features which make it a distinct and rare entity. He recognised that these tumours contained structures which occur only in the normal infundibular region, thereby providing landmarks for purposes of identification. In the normal tuber cinereum there is a system of blood vessels which had been previously termed the hypophysio-portal system by Popa and Fielding.[5] These vessels take origin from the sinusoids of the buccal portion of the hypophysis and from the capillaries of the neural portion, ascending through the stalk to the region of the infundibular recess of the floor of the 3rd ventricle, where they break up into a secondary capillary reticulum. In the course of their ascent, they acquire "glial" sleeves as far as the floor of the infundibular recess; at this point they lose these glial coverings and then continue as a capillary network. It is the presence of these unusual vessels that constitutes a "landmark" in the infundibular region. Globus also investigated the embryological and comparative anatomical structures analogous to this hypophysio-portal system since, according to Tilney,[6] the saccus vasculosus, which is represented by the dorsal saccular surface of an infundibular process, might in fact be the phylogenetic precursor of these bizarre tumours. Globus, however, was unable to come to any definite conclusion in this regard.

He reported 2 cases. Both patients presented typical signs of increased intracranial pressure, and both died within 48 hours after craniotomy. Necropsy was performed. Histological examination of the tumours revealed mainly elongated unipolar or bipolar cells, similar to the pituicytes found in the posterior lobe of the pituitary. Often these cells were aggregated into tracts of pseudo-fibres, and for this reason some investigators may have considered these tumours neurinomata or polar spongioblastomata. There were vascular channels described as "vascular lakes," and numerous vessels that were similar to those of the hypophysio-portal system. Among

the cells were numerous bodies bearing considerable resemblance to the colloid-like bodies found in the normal neurohypophysial region around the hypophysio-portal vessels.

Papez and Ecker[4] reported a case of infundibuloma associated with precocious puberty in an 8-year-old boy. Histological examination, performed after the boy had died on the 3rd postoperative day, revealed structures similar to those described by Globus, and the pathological diagnosis was in fact confirmed by the latter investigator.

Fine and Goldfarb[1] described a case of a 6-year-old boy, dying within 48 hours of craniotomy. Necropsy revealed a neoplasm similar in type to that described by Globus, with the characteristic "glial-sleeved" blood vessels and typical cellular elements.

It is interesting to note that in all of the above cases the patients showed unusual eye signs, including pathological movements and disturbances of vision, as did our patient.

CASE REPORT

Pat Mc., a boy 1 year of age, had been in reasonably good health until 3 months prior to admission, when he commenced vomiting and began to lose weight steadily. He vomited every feeding, sometimes in a projectile fashion, but retained a small portion. He was an extremely placid infant, but became rather irritable when moved suddenly. During this time he had been running a low grade of fever, associated with a slight cough. He had never been cyanosed or had convulsions, but had been constipated since birth. He weighed 8 lbs. 8 oz. at birth and on admission weighed 18 lbs. Three months before admission he had begun to support himself on his legs, but gradually ceased to do this, and in fact resented being forced to sit upright. He was less active than he used to be although he had never been a very active baby. He seemed to be in pain at times, rubbing the back of his neck and holding his head to the right. He had had rotatory eye movements since shortly after birth, and sometimes he made curious movements of his hands, the upper part of the arm being adducted, the elbow flexed, and the hands slowly pronating and supinating.

Birth History. He was a full term normal delivery, and had not been breast fed. He sat up at 6 months and cut his first tooth at 2 months.

Examination. He was a small baby lying very still, with an obviously enlarged head. The circumference of the skull measured 19½ inches. The anterior fontanelle was widely patent and tense.

He had marked rotatory nystagmus, worse on the right than on the left. There was a slight degree of rigidity of the neck and limitation of straight leg-raising. Muscle tone was good. Percussion of the skull revealed a "cracked-pot" sound over the temporal areas. A fluid thrill was also present in this region. No vascular bruits were heard. Reflexes were brisk; the right knee jerk was slightly brisker than the left. Bilateral Babinski response was present.

The right optic disc was pink and the margins were blurred with early papilloedema of 1 to 2 D. The left disc showed late and severe optic atrophy. Both pupils reacted very poorly to light.

Course. He continued vomiting, and parenteral fluids were administered. Ventriculography revealed a marked hydrocephalus. Both lateral ventricles were greatly dilated. There was no filling of the 3rd ventricle, but air did pass into the aqueduct and into the 4th ventricle, which was normal in size, shape and position. Destruction of the sella was noted. A rounded mass was seen elevating the tip of the left frontal horn and compressing the tip of the left temporal horn, suggesting an infundibular tumour with upward extension into the left frontal and temporal lobes.

Operation. Decompression of the ventricular system by needle drainage was done, affording adequate visualization of the anterior and middle fossae. On elevating the left temporal lobe

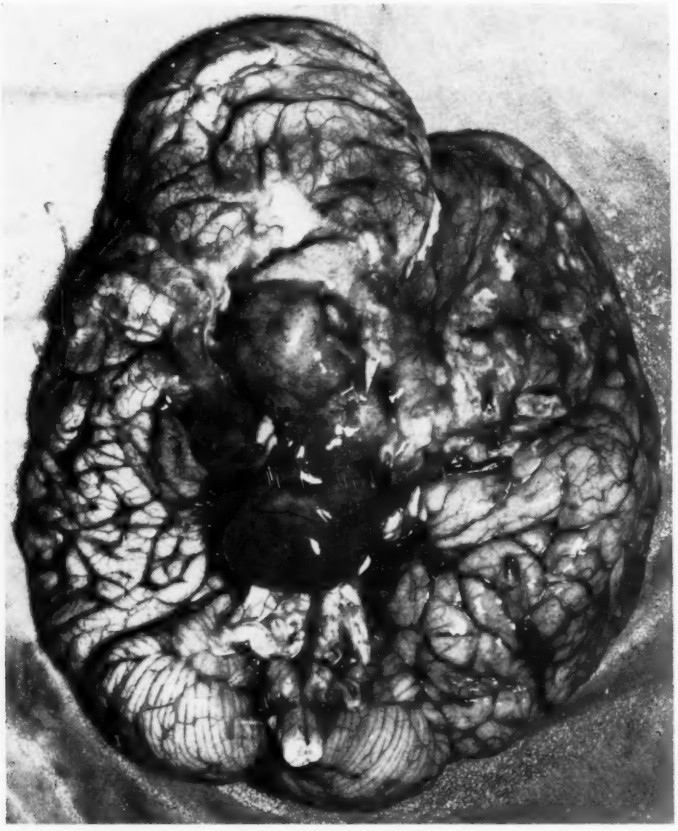

FIG. 1. Anteriorly and laterally towards the right side is the firm part of the tumour. Posteriorly and encroaching on the pons is the cystic portion.

a large tumour was seen extending medially and involving the entire 3rd ventricle. It was pale pink in color and appeared to be encapsulated with a rather tough transparent membrane. The tumour could be enucleated from the temporal lobe and followed toward the medial structures. An incision was made in the capsule and friable gelatinous material was evacuated, allowing better manipulation of the capsule. Because of extensive involvement, as much tumour as possible was sucked out. The presenting portion of the capsule was excised and closure of the craniotomy was accomplished.

Postoperative Course. The child was in coma with some degree of spasticity and had to be fed by tube. He had a febrile course for about a month, being treated with ACTH because of supposed pituitary deficiency. He died about 5 weeks after operation.

Autopsy. Gross findings. The brain collapsed considerably after removal from the cranial vault because of the escape of fluid from the ventricular system which had been distended by an internal hydrocephalus prior to death. The brain itself was soft, mushy, and almost gelatinous in consistency. Toward the inferior surface of the left frontal lobe was a yellowish area of degeneration at the site of the previous operative procedure. The tip of the left temporal lobe was involved by a mass of tumour.

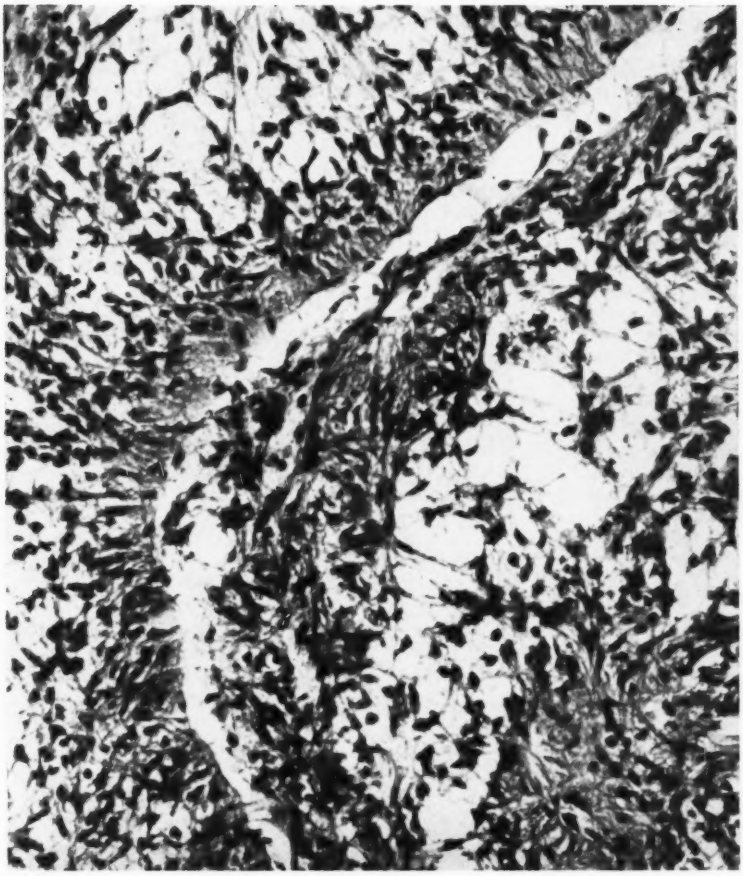

FIG. 2. Blood vessels in centre of photomicrograph demonstrate the palisaded nature of the surrounding glial cells. Fine cytoplasmic projections attach the cells to the wall of the blood vessels.

Retraction of the brain upwards, backwards and towards the right revealed a pinkish tumour with some grape-like clusters protruding outwards in the region of the infundibulum. The tumour involved the entire 3rd ventricle, bulging outwards and upwards between the antero-inferior portion of the frontal lobe and over to the right side. Removal of the brain revealed a large mass of tumour on the posterior part of the infundibulum, projecting forward. It was somewhat cystic and encroached upon the pons (Fig. 1). No evidence of recurrence of tumour was seen in the area of previous surgery.

Following fixation in formalin, re-examination of the brain demonstrated a large, greyish tumour, 5 cm. in diameter, involving the right hypothalamus and infundibular area. The tumour extended posteriorly to the anterior surface of the pons and inferior surface of the midbrain. In this region, it appeared to be cystic in nature and measured 1.5 cm. in diameter. Fine adhesions bound the tumour to the inferior surface of the cerebrum.

The tumour on the left side appeared closely adherent to and apparently infiltrated the inferior frontal gyrus.

Microscopic Description. The tumour was very vascular, being made up principally of dilated blood vessels, many of which were spiral in appearance (Fig. 2). They were bound by rather large palisaded cells with a fibrillary arrangement of fine cytoplasmic projections attaching the cells to the wall of the blood vessels and forming a halo-like effect. In other areas, the tumour was made up of small cystic endothelial-lined spaces with very little supporting tissue.

COMMENT

The location of the tumour, the age of the patient, and the gross and microscopic pictures are in keeping with Globus'[2] original description of an infundibuloma. There remains the possibility that the lesion could represent an unusual form of cystic astrocytoma.[3]

The authors wish to thank Drs. H. H. Pitts, C. J. Coady and J. Sturdy of the Department of Pathology for their help in preparing this material.

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COMBINED RETINO-CEREBELLAR ANGIOMATOSIS AND DEEP CERVICAL ANGIOMAS

CASE REPORT

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(Received for publication March 21, 1957)

I have been unable to find, after a thorough perusal of the literature, any case of retino-cerebellar angiomatosis associated with deep cervical angiomas. Worthy of note therefore is a case of such a syndrome which I have had occasion to study from a roentgenological point of view.

CASE REPORT

M.M. was a 26-year-old male with unremarkable familial anamnesis. At the age of 16 he noticed gradual and progressive dimness of vision, first of one eye and later of the other eye. In approximately 3 years the patient became blind. At the age of 24, i.e. 2 years before enter-

FIG. 1

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FIG. 2

ing the Neurological Institute of the University of Naples, subjective sensorial disturbances, characterized by tingling and numbness of the tips of the fingers, while reading by the Braille system, were noticed. These disturbances were then followed by severe pain, of radicular type, radiating from the nuchal region down into both upper limbs, much more so into the left one. Furthermore, symptoms and signs of increased intracranial pressure developed and the gait became impaired.

At the Neurological Institute the diagnosis of typical bilateral retinal angiomatosis was reached and the presence of a space-occupying lesion in the posterior fossa was strongly suspected. However, no satisfactory explanation for the radicular pains was given.

Plain roentgenograms of the skull showed no clear-cut signs of increased intracranial pressure. The calcified pineal gland was not displaced. In each orbit a linear, circular calcification was present, the size of which exactly reproduced the posterior and middle portions of the eyeballs (Fig. 1).

The left vertebral angiograms (Figs. 2 and 3) revealed the presence of at least two posterior fossa and two deep cervical angiomatous formations. The two intracranial angiomatous formations had the appearance of two homogeneous rounded sacs, the size of these being that of a bean, fed by branches of the posterior inferior cerebellar artery; no definite displacement of small vessels, surrounding these sacs, pointing to a possibly associated cystic tumor, was seen. The inferior portion of the basilar artery was pressed against the clivus. The anterior loop of the posterior inferior cerebellar artery did not descend beyond the foramen magnum. The two deep cervical formations were located at the level of and behind the posterior border of the body of the 3rd cervical vertebra. The upper one had irregular contours and was not homogeneously dense. Its size was that of a hazelnut. The lower formation, which more closely resembled the intracranial ones, was as large as a bean. Both structures were fed by branches of the vertebral artery and were drained, as clearly seen in the venous phase (Fig. 3), by a very peculiar bead-shaped vessel, directed upward, toward the base of the skull.

FIG. 3

In order to rule out the possibility of similar supratentorial lesions, right carotid arteriography was performed which showed only indirect signs of a slight internal hydrocephalus and an ophthalmic artery notably larger than the usual size.

Comment. It is my opinion that the brachialgic syndrome could be explained by the presence of the deep cervical angiomas, connected with the vertebral artery system. No operative check-up was done for the patient refused any surgical procedure and left the Clinic.

GLIOBLASTOMA MULTIFORME OF BOTH THE SEPTUM PELLUCIDUM AND THE CORPUS CALLOSUM

CASE REPORT

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Tumors involving both the septum pellucidum and the corpus callosum are infrequent. No clear-cut clinical syndrome has been associated with these neoplasms, and pneumoventriculography is essential in their identification. In those cases of either septal or callosal tumors disclosed only at postmortem examination, the diagnosis during life of the patient had been senile or pre-senile psychosis, general paresis or Korsakoff's psychosis.[7,9]

REPORT OF A CASE

A.A., a 55-year-old right-handed housewife, complained of a frontal headache which varied considerably in intensity for about 2 days. The next day it disappeared spontaneously,

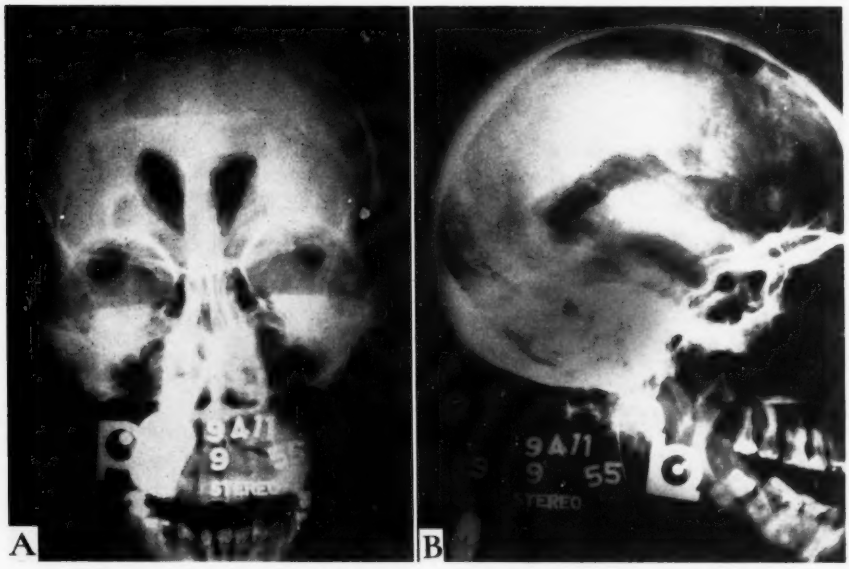

FIG. 1. Pneumoventriculograms. (A) Supine anteroposterior view. The septum pellucidum is diffusely widened, spreading the anterior horns. Note the slight depression and irregularity of the roof of the left lateral ventricle. (B) Prone left lateral view. There is a sharp curvilinear indentation into the anterior aspect of the roof of the lateral ventricle, with moderate dilatation of the body, atrium and temporal horns.

but returned with increased intensity after about 24 hours, together with vomiting, drowsiness and generalized weakness. She became uncommunicative and lapsed into sleep for periods of an hour or more. The following day she improved and was able to communicate with her surroundings, but within the next day her symptoms recurred.

There was no history of trauma, nor was there any antecedent infection. No alterations in personality had been noted by her family.

After admission to the hospital her fluctuating state of consciousness was conspicuous. At times she was drowsy and apathetic, tending to lapse into sleep. At other moments she was able to state her name and place of residence, but was disoriented for time and could

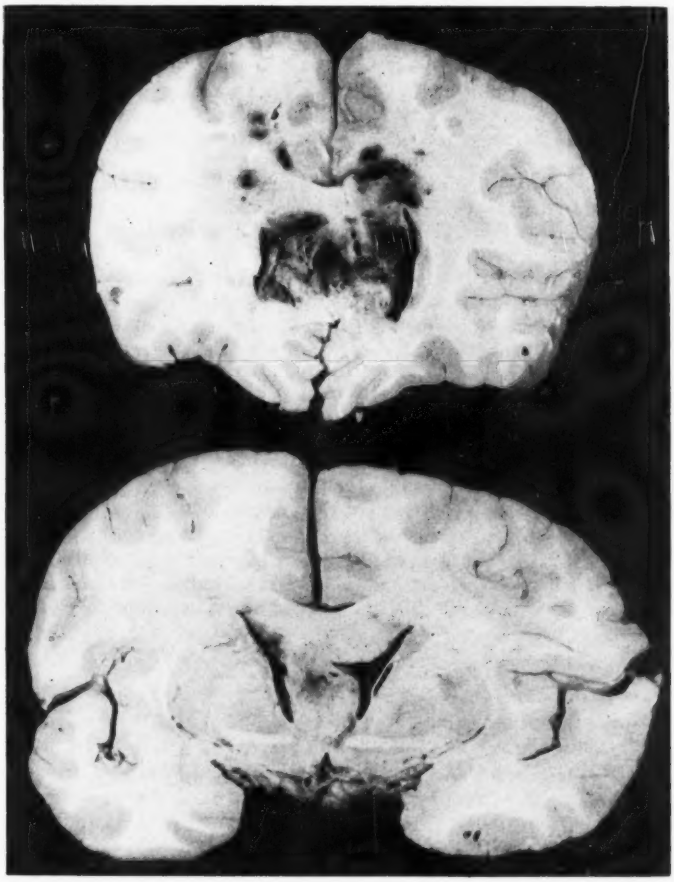

FIG. 2. (*Above*) Coronal section of the brain through genu of the corpus callosum. Hemorrhage is present within the tumor which is spreading the tips of the lateral ventricles and extending into the left side of the corpus callosum.

(*Below*) Coronal section through junction of the anterior portion and body of the lateral ventricles. Note the tumefaction of the septum pellucidum and extension of neoplasm into the inferior aspect of the corpus callosum. There is slight irregularity of the roof of the right lateral ventricle and a downward bulging of the roof of the left lateral ventricle.

perform only the simplest acts and calculations. Her attitude was one of complete indifference with flattening of all emotional expression.

On physical examination no motor or sensory defects could be demonstrated, nor were there any pathologic reflexes. The left pupil was slightly larger than the right. Pupillary reactions, ocular movements and optic fundi were all normal. A slight facial asymmetry with flattening of the left side of the face during mimetic movements was noted.

Lumbar puncture disclosed an initial pressure of 260 mm., which fell to 200 mm. after removal of 8 cc. of clear fluid. No cells were present, and total protein, sugar and chlorides were normal. The peripheral blood and urine were normal. Plain roentgenograms of the skull showed no bony change or abnormal calcification. The sella turcica was normal. The pineal body was in the midline, but was displaced slightly posteriorly and downwards.

Because of her somnolent and deteriorating condition, bilateral burr holes were placed for a possible subdural hematoma. No blood was encountered, but the brain was under markedly increased pressure. Therefore, ventriculography was performed, 10 cc. of air being injected into each lateral ventricle. The frontal films (Fig. 1A) revealed the lateral ventricles to be slightly dilated and in the midline. The roof of the left lateral ventricle was slightly irregular and flattened. The septum pellucidum was conspicuously widened, measuring over 1.5 cm. On the lateral films (Fig. 1B) an arcuate impression about 4 cm. in length was noted in the anterior aspect of the roof of the left lateral ventricle. A similar but less conspicuous indentation was identified in the right lateral ventricle. It was believed that the mass within the corpus callosum was continuous with the obvious septal tumefaction.

Since the tumor was considered inoperable, palliative ventricular drainage through the burr holes was instituted. The next day the patient improved considerably. As the drainage diminished she again lapsed into deep sleep. A right subtemporal decompression was performed, but she expired the next day in deep coma with fixed, dilated pupils.

Autopsy (Fig. 2). As disclosed by needle biopsy at the time of ventriculography and postmortem examination, the tumor was a glioblastoma multiforme. On coronal section of the brain at the level of the body of the lateral ventricles, the septum pellucidum was replaced by pinkish-grey, hemorrhagic tumor which merged imperceptibly with the anterior two-thirds of the corpus callosum, leaving only a thin strip of normal tissue among the most dorsally situated fibers. The tumor spread the inner aspects of the bodies of the lateral ventricles, and indented their roofs. At its broadest point the septum pellucidum measured 2 cm. The foramen of Monro was occluded by tumor. The mass involved the cingulate gyrus on the left and the fornix bilaterally, obliterating the normal topography. Extension into the adjacent centrum semiovale was observed, but the basal ganglia were uninvolved. Sections through the brain stem revealed hemorrhagic extravasations in the periaqueductal grey matter and tegmentum of the midbrain extending into the central portion of the pons. The hypothalamus was not involved.

DISCUSSION

Tumors of the septum pellucidum are rarely recognized clinically, French and Bucy[6] having found descriptions of only 31 cases in the literature. In reporting 5 cases of their own, the authors emphasized the fact that a significant number of these lesions were benign, subependymal astrocytomas and were surgically accessible. The presenting symptoms varied in duration from as little as 2 weeks to 7 years. Headache and visual disturbances were the most common complaints, followed by disturbances of memory, mood and initiative, especially with lesions invading the frontal lobes and corpus callosum. Less frequently, weakness, unsteadiness, seizures and cataleptic-like states occurred. The paucity of localizing signs was striking.

A glioblastoma multiforme of both the anterior half of the corpus callosum and the septum pellucidum was reported by Dyke and Davidoff[5] in a 43-year-old woman who complained of severe headache and tinnitus followed by projectile vomiting, confusion, and incontinence of urine. Adiadokokinesis and apraxia were

present bilaterally with reflex and sensory changes on the left. Bilateral papilledema was present. The spinal fluid was xanthochromic. Ventriculography disclosed separation of the anterior two-thirds of the bodies of the lateral ventricles and only the posterior portion of the 3rd ventricle was visible.

Bailey[2] reported a similar case in which the neoplasm extended into both frontal lobes, pushing the 3rd ventricle backwards and reducing the anterior horns of both lateral ventricles to slits.

Chusid and de Gutiérrez-Mahoney[3] recently collected an additional 20 cases of septal tumors, adding one of their own. Their patient, a 72-year-old woman, was ill only 3 weeks. Changes in personality and vomiting were the only indications of cerebral abnormality. At autopsy the tumor, a glioblastoma multiforme, was found to involve the entire septum. It projected into the left lateral ventricle and compromised both interventricular foramens. The neoplasm probably originated in the septum at its juncture with the corpus callosum, and had spread into the callosal fibers inferiorly. The frequency of invasion of the frontal lobes by callosal tumors was emphasized by Alpers and Grant.[1]

Mental changes in the inaugural phase of tumors of the corpus callosum were noted by Schlesinger.[5] Disturbances in memory were more common with lesions of the splenium while affective behavior, particularly lack of drive and euphoria, was disturbed more commonly with tumors of the rostrum and genu.

Usually the radiologic diagnosis of tumors of the septum pellucidum and corpus callosum is made by means of pneumoencephalography. The widened septum pellucidum bulges asymmetrically into the lateral ventricles, which may dilate if the flow of cerebrospinal fluid is obstructed. Irregularity and truncation of the anterior horns of the lateral ventricles and displacement and deformity of the 3rd ventricle may appear. The septum pellucidum occasionally may be smoothly and diffusely widened, presenting an appearance similar to that of noncommunicating cysts.

Tumors of the corpus callosum impinge on the roofs of the lateral ventricles, and may extend down the genu of the corpus callosum. The lateral ventricles may be separated by tumor insinuating between the anterior horns. Such a spreading of the lateral ventricles may simulate a lesion of the septum pellucidum.

The present case provides the unusual combination of an almost symmetrically widened septum pellucidum together with a definite indentation into the roofs of the lateral ventricles. This pneumoencephalographic pattern has not been described either in previously reported cases of tumors or cysts of the septum pellucidum or of tumors of the corpus callosum. The necropsy findings clearly accounted for the unusual roentgenographic pattern by showing extension of the tumor from the thickened septum pellucidum into the tumefied corpus callosum. Whether the tumor originated in one location or the other could not be ascertained since the involvement of both was equal.

In differential diagnosis one would have to consider lesions such as agenesis or lipoma of the corpus callosum, both of which produce distortions of the lateral and 3rd ventricles easily differentiated from the picture seen in our patient. Other pathologic states that might be thought of are tumors originating in the falx cerebri, the olfactory groove and the anterior lobes close to the midline. Tumors arising within the lateral ventricles, some midline bilateral parasagittal masses, and cysts of the cavum septi pellucidi and cavum vergae are other possibilities.[4] Tumors of the splenium of the corpus callosum cause a characteristic widening of the posterior aspects of the lateral ventricles in addition to depression of these structures.[5]

Gliomas of the corpus callosum and septum pellucidum reach such size before they become manifested clinically that it is doubtful if anything except palliative decompression and radiation therapy can be provided. While astrocytomas confined to the septum pellucidum have been excised with good results,[6] the more frequent malignant tumors produce symptoms after extending into surrounding areas. The blocked ventricular system in an acutely ill patient may be drained as a temporary measure. Subtemporal decompression may provide longer relief and allow radiation therapy to be given. Needle biopsy of the lesion is sometimes obtainable during bilateral ventricular puncture. Transcortical or transcallosal exploration for biopsy or for removal of sufficient neoplasm to effectively decompress the occluded interventricular foramen is unjustifiably hazardous in acutely ill patients.

SUMMARY

A specific diagnosis of tumor of the septum pellucidum, corpus callosum or both usually cannot be made on clinical grounds alone. All share a common constellation of symptoms caused primarily by increased intracranial pressure. However, involvement of the adjacent frontal lobes, cingulate gyri and fornix may contribute to the symptom complex. Headache and vomiting appear early, followed by apathy, confusion, disorientation, loss of memory and a fluctuating state of consciousness with few localizing or lateralizing signs of value. A striking loss of spontaneous expression and indifference may be present. Apraxia is of distinct value but may be difficult to elicit. The diagnosis can be established by pneumoencephalography. Separation of the lateral ventricles by a thickened septum pellucidum, distortion of the roofs of the lateral ventricles and deformity of the 3rd ventricle are distinctive features. The majority of such neoplasms are malignant gliomas which are inaccessible surgically.

A case is reported in which there was simultaneous tumefaction of the septum pellucidum and the corpus callosum.

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A SIMPLE ARRANGEMENT TO FACILITATE TIDAL DRAINAGE

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(Received for publication February 6, 1957)

The use of tidal drainage for patients with injuries of the spinal cord is commonly accepted. In our neurosurgical department we have used the apparatus designed by Donald Munro.[1] This apparatus has a hypodermic needle as an air vent, and in most instances it has worked quite well.

However, there are some possibilities of functional failure. Munro mentioned several of these, among which the premature breaking of the siphonage because of the

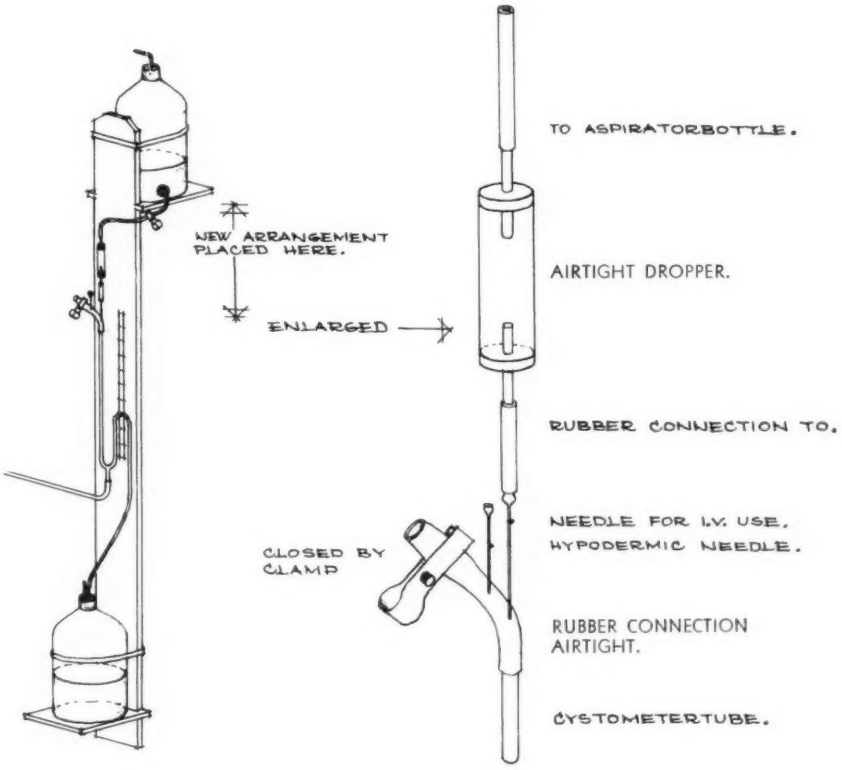

FIG. 1. *Left:* Drainage apparatus after Munro. *Right:* New dropper-system.

* Chief: C. F. Bisgaard-Frantzen, M.D.

application of an overdimensioned air vent or too large a rubber tube for the siphon is the most important, and our experience confirms this. But we found that the siphonage has been broken more frequently in another way. In the original apparatus a water trap often is formed in the cystometer tube, so that when the bubbles come to the siphon they may start an abortive emptying in the resting phase, while in the working phase they break the siphonage too early. The trap is made when the drops from the reservoir continue as drops to the cystometer tube with only intermittent admission of air.

Since we started using the arrangement shown in Fig. 1, the apparatus has from the very first moment been working without any trouble. (It is our experience that the usual arrangement demands several hours to fall into rhythm.) The principle is very simple. The falling drops in the inserted needle are converted into a regular flow running along the inside of the cystometer tube to a fluid level at the bottom. The air is given free admission to the tube through the air vent.

This simple arrangement, which any one can duplicate, has proved to be perfect without disturbing the structure of the original apparatus, and it deserves—in our opinion—to be commonly used by all with similar problems and difficulties of tidal drainage.

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IMPROVED LOWER-LIMB NEGATIVE-PRESSURE EQUIPMENT FOR THE REDUCTION OF CEREBRAL BLOOD PRESSURE IN NEUROSURGERY

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(Received for publication March 25, 1957)

Equipment has been described by James *et al.*[1] which uses negative pressure to effect pooling of the blood in the lower limbs, after the blood vessels have been dilated by administration of drugs.

The units described in this note were designed and manufactured at the request of the Neurosurgical Department of the Auckland Hospital, and have been in use since 1953.

DESCRIPTION OF EQUIPMENT

1. *Negative-Pressure Chambers.* This unit comprises two "Perspex" cylinders (Fig. 1), one fitting over each leg. It is designed this way for lightness, to facilitate setting up, and to provide complete and unobstructed visibility of the legs. The open end of each tube is sealed by a "Celeron" plastic end-plate, especially machined to take a short rubber sleeve with which the seal around the legs is effected.

The tubes are 9 inches in diameter to give comparative freedom of foot movement, and for convenience of manufacture are not tapered. The thickness of the wall is $\frac{1}{4}$ inch and the over-all length is 3 feet. For purposes of design these tubes can be treated as short thin-walled cylinders. Thus with the ultimate tensile strength of plasticised "Perspex" at 3 tons/sq. in. and the tubes subject to a maximum vacuum (15 lbs./sq. in.) the factor of safety is well in excess of 6, the normal factor of safety for alternating load applications.

The longitudinal joint is tongued, grooved and cemented, and the closed end of the tube is domed for extra strength. The tubes are strengthened at the points of connection by cemented bosses. The points of connection can be seen in Fig. 2, the tubes being interconnected by a preformed rubber bend.

In each tube a special port is provided, designed and positioned to facilitate rapid application of a drip set to either leg.

2. *Connectors.* The connectors are screwed-brass rubber-tube adaptors of conventional type. They are tightened by hand in the connector bosses, an "O" ring, recessed into the adaptor, effecting the seal against the face of the boss. The connectors and the vacuum gauge adaptor are readily interchangeable in the bosses. The dimension of the tube adaptor permits an easy-push fit for 9/16 inch I.D. thick-walled rubber vacuum hose.

3. *Tube and Leg Sealing End Plates* (Fig. 2). These end plates are machined from $\frac{1}{2}$ inch thick "Celeron," a fabric-reinforced plastic sheet. They spigot into the "Perspex" cylinders, the seal at this point being effected by a sponge-rubber ring, of rectangular cross section, cemented to the plate. They are fastened to the cylinders by two diametrically opposed quick-acting toggle clips. In Fig. 4 it may be seen that the aperture in the plate for the leg is machined off-centre. This is to enable the leg to be more comfortably positioned as each plate can be rotated to offer the least amount of pressure against the leg. This rotation does not upset retention of the clip, for the groove in the plate in which the clip engages is continuous. There are three sizes of end plates—5, 6 and 7 inch—and in each size the aperture for the leg is offset so that the distance between the peripheries of the aperture for the leg and the end plate remains the same.

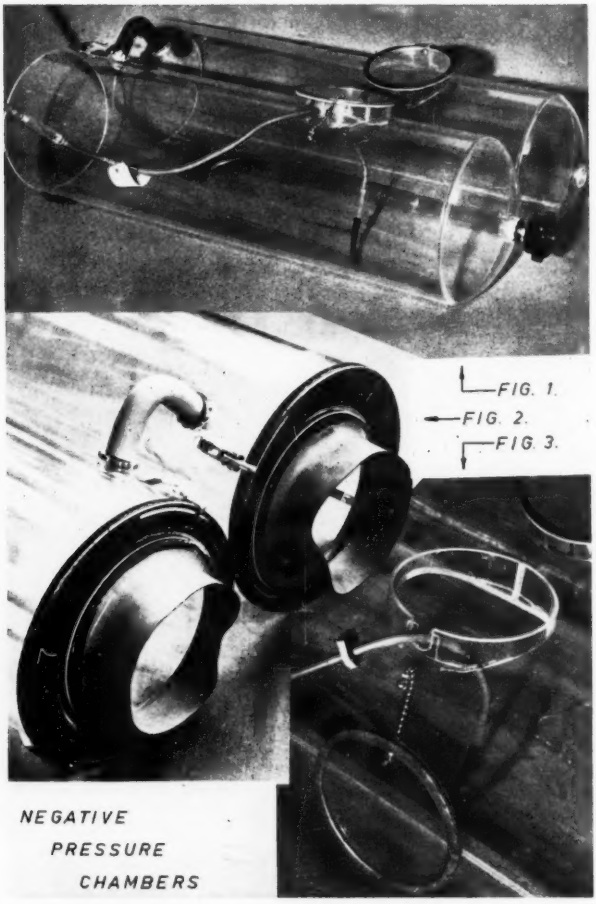

FIG. 1. View of cylinders coupled up as for an operation with drip set in position.
FIG. 2. View of end plates fitted.
FIG. 3. Drip access ports.

The leg-sealing sleeves are 1/16 inch thick soft rubber 3 inches long, one inch less in diameter than the aperture for the leg and have a square section of rubber ring vulcanised to their outside surface at one end. This end is stretched over the lip of an annular ring machined concentric with the aperture in the end plate and is retained positively by a garter-type tension spring.

4. *Drip-Set Access Ports.* These ports, each equipped with a detachable lid, are $6\frac{1}{2}$ inches I.D. to provide adequate access of the hand and also to enable a standard saline drip bottle to be passed through if necessary. As a precaution against loss, the lids are retained to their respective "Perspex" cylinder by a length of ball chain. The lid seal is effected by a sponge-rubber ring in the same manner as the end-plate seal. The drip-set tube seal is very simply effected, and is shown clearly in Fig. 3. The D-shaped sponge-rubber seal is slit to the hole for

ease of application around the drip-set tube, and is prevented from being drawn inwards under suction by a backing plate cemented to the inside surface of the port. The cylinder not accommodating the drip set has the drip-set recess blanked off with a plain D-sponge seal.

5. *Negative-Pressure Source.* The modified vacuum cleaner unit used to obtain the negative pressure has proved to be most satisfactory. Similar units have, as a result, been used since

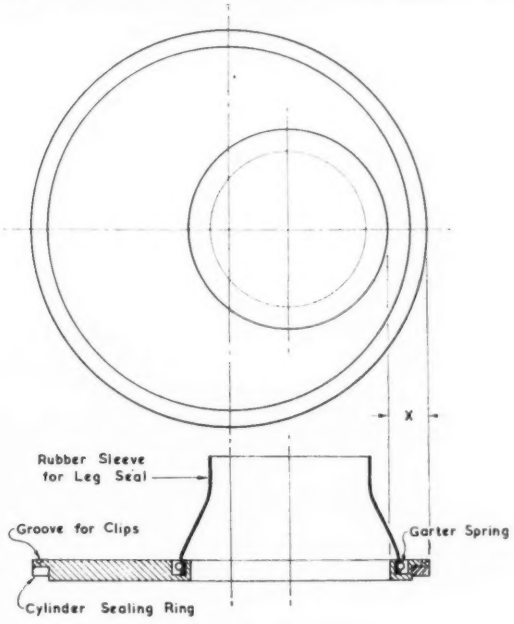

FIG. 4. Section of end plate.

in other projects such as respirators, exhausters, etc. with success. The unit is simply a shortened standard horizontal household vacuum cleaner. The shortening is effected during manufacture by dispensing with the normal filter compartment. The double-stage pump itself is highly efficient and of ample capacity, and a maximum vacuum of 4 inches of mercury is attainable. The unit is connected directly to the negative-pressure cylinders by 15 feet of 9/16 inch I.D. thick-walled vacuum hose so that when pumping it can be remote from the actual operation to reduce noise. The noise level is quite low however, since for the normal negative pressure required the motor speed is reduced.

The motor and pump speed and thus the negative pressure in the cylinders is controlled by means of a "Variac" variable transformer in the motor circuit. The "Variac" is positioned near the gauge on the cylinder, so that the negative pressure can be observed and readily varied by the anaesthetist.

METHOD OF FITTING

1. Assess the size of the patient's legs at the upper thighs to determine the appropriate size of end plates to use.
2. Pass the end plates, rubber sleeve preceding, up the legs. (See note below.)
3. Position the end plates as far up the thighs as convenient, ensuring that the rubber

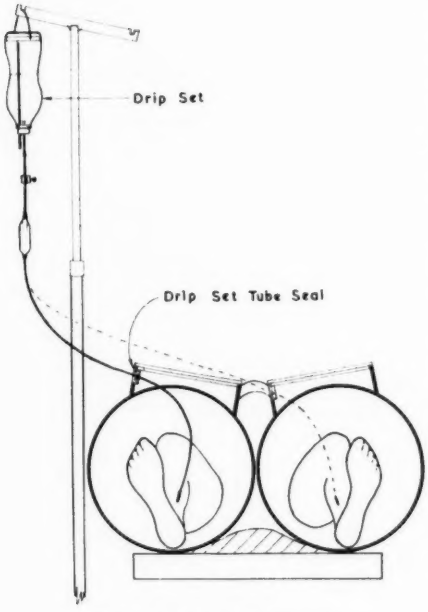

FIG. 5. Drip-set arrangements.

sleeves, extended fully toward the hips, fit neatly and are not too constrictive. The end plates should also be rotated to the most comfortable position for the thighs. This will be with the narrowest portion of each plate to the bottom and slightly inwards. Place packings under the patient to relieve excessive pressure of the plates on the legs.

4. Tape the rubber sleeves to the legs, using 2–3 inch wide elastic adhesive tape. Effect the taping as high as possible on the thighs.

5. The "Perspex" cylinders are then passed up the legs. The cylinders are not identical, as the ports are positioned to give the best approach for the drip set (Fig. 5).

Note: If a drip set is already in use, the bottle is first passed through the end plates (see 2 above), then along inside the appropriate cylinder and up through the port just before the leg is introduced. Alternatively the drip set could, with care, be disconnected and refitted through the port after the cylinders are in place.

6. With the "Perspex" cylinders close to the end plates, attach the interconnecting rubber bend to the tube adaptors, rotating the cylinders to line up as required.

7. Engage the toggle clips into the groove of the end plates and fasten to effect the seal.

8. Lay the drip-set tube into the recess provided in the port. Fit the D-sponge-rubber seal around the tube and press the seal into the recess ensuring that a good seal is effected and that the drip-set tube is nicely positioned without kinks. Fit the port lid. For the other drip-set port which is not being used, fit a plain D-sponge seal into the recess and attach the port lid.

9. The vacuum tube is now connected to the cylinder nearer to the pump unit, the pressure gauge being fitted to the other cylinder. The control "Variac" is conveniently placed near the gauge.

10. Evacuation may now be commenced, regulating the negative pressure by means of the "Variac." The cylinders may be strapped together and to the operating table if desired, but it is preferable merely to leave the cylinders free to move, at least endways, so that as the suction is applied, the patient is not drawn into the cylinders, but the cylinders move over the patient. The cylinders are light enough to do this if not restrained.

OPERATIONAL ASPECTS

The degree of reduction of pressure attained in different patients either by administration of drugs or by the use of the special equipment, varies, though in general more reliance can be placed on the latter method. There is, however, a fairly well defined "plateau" in the pattern of pressure reduction attainable by the use of intravenous drugs. It is beyond this "plateau" that the negative-pressure system operates so successfully. For instance, in a "resistant" individual with a normal systolic blood pressure of 120–125 mm. mercury, drugs may reduce the pressure to only 90–100 mm. mercury. If the negative-pressure system is now operated, a further

drop to about 60 mm. mercury is very rapidly attained. This is the lowest pressure normally used with safety, but if necessary in an emergency, such as a rupture of an aneurism occurring during an operation, the pressure can be lowered rapidly still further to 30 mm. mercury, to permit surgical repair. This extremely low pressure must be maintained for a very brief period only, to minimise the risk of permanent brain injury.

The pressure can be raised very rapidly by removing the negative pressure. This is not possible either with drugs or by posturing.

Since 1953 it has become increasingly evident that the hazards of an operation demanding extreme head-up posture are less when the negative-pressure system is used. If posturing is employed to effect the required changes in pressure, an undesirable re-arrangement of lights and equipment results, and the surgeon and staff are unnecessarily impeded in their work.

SUMMARY

A new design of negative-pressure equipment is described. The apparatus is transparent so that the condition of the leg and blood vessels can be observed. It is light, simply fitted and positive sealing can be effected. Special ports are provided to permit intravenous therapy or blood transfusion in either leg.

REFERENCE

1. James, A., Coulter, R. L., and Saunders, J. W. Controlled hypotension in neurosurgery with special reference to hypotension induced by pneumatic suction applied to the legs. *Lancet*, 1953, *1:* 412–416.

NOTICES

CONGRESS OF NEUROLOGICAL SURGEONS—PLACEMENT SERVICE

Response to a questionnaire recently sent out by the Survey Committee of the Congress of Neurological Surgeons indicates a majority of neurological surgeons in favor of establishment of a placement service. A limited placement service for neurological surgeons has been set up by the Survey Committee. All neurological surgeons who desire a new partner or associate are invited to participate. A list of the men offering positions will be compiled and revised as often as necessary. This list will be sent on request to those men who are looking for new positions. The list of available positions will be sent only to individuals who have completed residency training or have started their final year of neurosurgical residency training. Contact between individual neurological surgeons will be initiated by those seeking the positions. The Survey Committee will not participate in individual contacts and arrangements, and will not be responsible for unsatisfactory placements. No charge will be made for the service. All inquiries should be directed to the chairman of the Survey Committee, Dr. John R. Russell, 1100 W. Michigan Street, Indianapolis 7, Indiana.

MEETINGS

American Academy of Neurological Surgery, The Cloister, Sea Island, Georgia, November 11–13, 1957. Dr. Eben Alexander, Jr., Bowman Gray School of Medicine, Winston-Salem, N. C., Secretary.

American Neurological Association, Claridge Hotel, Atlantic City, New Jersey, June 16–18, 1958. Dr. Charles Rupp, 133 South 36th St., Philadelphia 4, Pa., Secretary.

Association for Research in Nervous and Mental Disease, Hotel Roosevelt, New York, N. Y., December 13–14, 1957. Dr. Rollo J. Masselink, 700 West 168th St., New York 32, N. Y., Secretary.

Brazilian Neurosurgical Society, São Paulo, Brazil, December 14, 1957. Dr. José Geraldo Albernaz, Secretary.

Congress of Neurological Surgeons, Statler Hotel, Washington, D. C., November 7–9, 1957. Dr. Philip D. Gordy, Suite B-1, Professional Bldg., Wilmington, Del., Secretary.

Harvey Cushing Society, Mayflower Hotel, Washington, D. C., April 21–23, 1958. Dr. David L. Reeves, 316 West Junipero St., Santa Barbara, Calif., Secretary.

Neurosurgical Society of America, Key Biscayne, Florida, January 15–18, 1958. Dr. Frank P. Smith, 260 Crittenden Blvd., Rochester 20, N. Y., Secretary.

New England Neurosurgical Society, Boston, Mass., November 22, 1957 (in conjunction with the New York Society of Neurosurgery). Dr. Joseph F. Dorsey, 270 Commonwealth Ave., Boston 16, Mass., Secretary.

New York Society of Neurosurgery, Boston, Mass., November 22, 1957 (in conjunction with the New England Neurosurgical Society). Dr. Henry Wigderson, 162-05 89th Ave., Jamaica 32, N. Y., Secretary.

Pan-Pacific Surgical Association, Honolulu, Hawaii, November 14–22, 1957. Dr. F. J. Pinkerton, Room 230, Young Building, Honolulu, Hawaii, Director General.

Society of British Neurological Surgeons, Wassenaar and Utrecht, Holland, May 8–10, 1958. Mr. D. W. C. Northfield, London Hospital, London E. 1, England, Secretary.

Southern California Neurosurgical Society, Del Monte Lodge, Del Monte, Calif., February 28–March 2, 1958 (in conjunction with the San Francisco Neurological Society). Dr. Robert H. Pudenz, 744 Fairmount Ave., Pasadena, Calif., Secretary.

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